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ORIGINAL ARTICLES

CONGENITAL ANOMALIES

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I AM greatly honored by the Award which the American Academy of Pediatrics has bestowed upon me and I am certain that this recognition of our studies will stimulate my co-workers and myself to further efforts in the line of work which we began about 12 years ago.

I have repeatedly had the privilege of presenting our experimental work to meetings of the American Academy of Pediatrics and it is not necessary, therefore, to describe to you again in detail the congenital anomalies induced in animals by maternal dietary deficiency. It seems preferable to give you today a brief summary of the general aspects and results of our studies and to present to you some of the conclusions which may be drawn from them.

The incentive to our experimental work was a marked interest in congenital anomalies of children. Adverse factors acting in prenatal life contribute appreciably to the mortality of infants and many children go through life deformed or crippled because of unfavorable intrauterine conditions. Congenital anomalies are at the root of many chronic and of some intractable diseases of childhood, a fact which is brought out with increasing certainty by improved diagnostic methods. Without going into details I wish to point out how many congenital anomalies of the urinary tract are now recognized *intra vitam,* which only one or two decades ago puzzled us by their nonspecific symptoms. Congenital anomalies of the intestinal tract which were previously diagnosed as "vomiting," "malnutrition," etc., are now better understood and often accessible to surgical treatment. Anomalies of the cardiovascular system are more conspicuous and they were early recognized as such; in recent years congenital anomalies of the blood vessels have been described in increasing number, some of them associated with other congenital anomalies. An analysis of the endocrine disorders of childhood reveals that many of them are due to prenatal maldevelopment of a gland with internal secretion. Anomalies of the central nervous system

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are numerous; they respond poorly to surgical treatment and contribute to the problem of mental deficiency of childhood. In addition to gross anomalies there is an increasing knowledge of histologic and chemical congenital anomalies which give rise to diseases of children.

This brief outline will suffice to make understandable the interest of a pediatrician in teratologic research. Although pediatric surgery has made substantial progress in recent years in the correction of many congenital anomalies, it will be generally admitted that prevention of such prenatal errors must be our final aim. This leads to the question of the etiology of congenital anomalies.

There can be no doubt that many congenital anomalies are hereditary, i.e., genetically determined. They appear in families and are transmitted according to the laws of heredity. So much work has been done in the field of hereditary congenital anomalies that at one time it was widely believed that all congenital anomalies are genetically determined. Until recently there was little proof that—in mammals and man—congenital anomalies can be caused by adverse environmental factors acting after conception. There was a need for an experimental method of inducing congenital anomalies in small mammals by means of controllable environmental changes. Large numbers of experiments could then be carried out to yield reliable conclusions. When Dr. Rose Nelson and I began these experiments, we thought chiefly of two methods to achieve this goal. We tried to interfere with the normal intrauterine development of rat embryos by (a) changing their endocrine environment and (b) by changing their nutritional supply. With the second type of experiment we had success. One can disturb the normal development of the embryo by depriving the pregnant female of certain essential nutritional elements. General starvation of the mother results in sterility, abortions or stillbirths. This was shown in man in Holland, Greece and Russia during the last war and similar observations had been made previously during periods of famine. Comparable results are usually obtained in animal experiments when quantitative or qualitative dietary restrictions are imposed upon the mother. However, under special experimental conditions, when the pregnant animal is kept in a borderline state of depletion of a specific nutritional element, the embryo may be damaged without being killed. Under such circumstances congenital anomalies may appear in the offspring. In our experiments congenital anomalies could be induced in rats whose mothers had been deprived of riboflavin, vitamin D or vitamin A. One of the most interesting and surprising facts was that maternal depletion of a specific factor results in specific congenital anomalies. Thus lack of vitamin D causes bowing of the bones of the forearms and legs. Lack of riboflavin results in a different pattern of skeletal changes, such as cleft palate, syndactylism, fusion of ribs and shortening of the jaw and of the bones of the forearms and legs. Lack of vitamin A affects essentially development of soft tissues and leads to anomalies of the eye, the heart, the diaphragm, the kidneys and other urogenital organs. There is no overlapping of anomalies in these different patterns which are specific for the mother's deficiency. These experiments, though technically difficult, have been repeated by various investigators, particularly by Dr. James G. Wilson, who contributed greatly to the analysis of the anomalies of the urogenital and cardiovascular systems induced by vitamin A deficiency.

What conclusions can be drawn from these experiments?

Let me state at first that in none of our studies did we try to simulate human dietary conditions and that we do not think that in the United States dietary deficiency of mothers is a factor in the etiology of congenital anomalies. However, in populations which are

restricted in their food supply by isolation, customs or environmental peculiarities, conditions may arise which are comparable to our animal experiments. Endemic cretinism caused by maternal iodine deficiency is a case in point.

Any further interpretation of our experimental results will be facilitated by a distinction between "dietary deficiency" of the mother and "nutritional deficiency" of the fetus, since nutritional deficiency of the fetus may have other causes than dietary deficiency of the mother. We think of metabolic disorders of the mother, diseases of the placenta, or pathologic changes of the blood vessels which could lead to nutritional disturbance of the fetus in spite of a proper diet of the mother. Infectious agents may interfere with the nutrition of the embryo by damaging its vascular supply. Gregg thought that rubella in early pregnancy leads to congenital anomalies by action upon embryonic blood vessels and malnutrition of the organs in formation.

We consider the production of congenital anomalies by maternal dietary deficiency merely as an experimental method which permits interference with the normal development of the embryo and thus reveals specific nutritional requirements of organs and organ systems which can not be detected otherwise. This is of importance, since the formation of the newborn child from a single cell, the zygote, involves innumerable chemical reactions which are so far not accessible to direct observations in mammals and in man. However, the normal or abnormal course of these reactions determines whether a normal or an abnormal trait develops. We know that the developmental processes are directed by the genetic material contained in the germ cells and that the building material required for differentiation and growth of the embryo is derived from the mother. Thus the normal development of the growing organism depends upon a sound inheritance as well as upon a proper environment. When a gene is defective the chain of developmental processes may be altered and the embryo become deformed or die. Similarly the normal development can be interrupted by a defective supply of nutritional elements from the mother, the results being the same, embryonic malformation or death. It is not difficult to assume that the same developmental process is altered in one instance by the presence of an abnormal gene, in another instance by absence of a necessary chemical substance which is normally supplied by the mother. The result would be the same in both cases. This concept gives us a plausible explanation for the established fact that similar or identical malformations may be genetically determined and hereditary in one case and accidental and nonhereditary in another.

Nutritional experiments like ours have demonstrated that environmental changes can bring about types of congenital anomalies which had been known to be hereditary in other instances. Thus stocks are known in which cleft palate, syndactylism or coloboma of the retina are transmitted genetically. These are anomalies which can be produced experimentally as nonhereditary phenocopies by maternal riboflavin—or vitamin A—deficiency. The nutritional experiments permit a glimpse into some of the chemical processes which take place in the embryonic development of the affected organs. Such knowledge is needed in embryology as well as in genetics. The modern geneticist is interested in the mechanisms of gene actions and any insight into the chemistry of development is of value to him. It is a matter of satisfaction to us that there is no contradiction between our experiments concerned with environmental changes leading to malformations, and the newer concepts of the science of genetics.

The pediatrician will be interested in the fact that not all congenital anomalies are hereditary and in the demonstration that similar anomalies may be hereditary in one and

nonhereditary in another case. Such knowledge will temper his eugenic advice when he is interrogated about the advisability of parenthood. Our knowledge in this field is still limited and it is usually difficult to determine the origin of congenital anomalies in a specific case. However, progress is being made in the recognition of hereditary anomalies as well as in those of environmental origin and eugenic advice will rest on a firmer scientific basis in the future.

Finally I wish to emphasize that our experiments were made possible by relatively recent discoveries in the field of nutrition. It was by depletion of vitamins, latecomers in the list of necessary foodstuffs, that congenital anomalies could be produced experimentally. Progress in the science of nutrition had to precede progress in our concepts of congenital anomalies, thus demonstrating again the close interrelationship of different fields of research.

I wish to thank you again for the honor of giving me the Borden Award of 1950.

SPANISH ABSTRACT

Anomalías Congenitas

El autor analiza el periodo en el cual la teoría prevalente aceptaba el origen genetico pre-determinado de las anomalias congenitas. La hipotesis sosteniendo que factores ambientales actuando después de la concepción podian causar anomalias en el desarrollo en mamiferos y en el hombre, carecía de verificación experimental. El descubrimiento y aplicación de un metodo basado en la restricción de ciertos elementos esenciales de la dieta para la producción de malformaciones en ratas, hizo posible la comprobación experimental de esta hipotesis. El autor discute aspectos adicionales de estos resultados experimentales, señalando que la naturaleza especifica de estas restricciones dietarias destaca su importancia en el estudio de la quimica del desarrollo.

Ellard Avenue and Bethesda

COMPARISON OF PULMONARY HYALINE MEMBRANES IN VAGOTOMIZED RABBITS WITH THOSE IN NEWBORN INFANTS

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THAT the hyaline membranes seen in the lungs of newborn infants are produced by aspiration of vernix caseosa or amniotic sac contents is a widely accepted theory at the present time. Recently some doubt has been cast on the validity of this theory.[1,2] The fact that fat and cornified epithelial cells can not be demonstrated in the hyaline membranes in all cases makes it difficult to consider aspiration of vernix caseosa as a responsible factor. The absence of large numbers of cornified epithelial cells in the presence of heavy concentrations of hyaline material in the alveoli and alveolar ducts also raises a serious question as to the role of aspirated amniotic sac contents in the production of these hyaline membranes. While the aspiration of vernix or amniotic sac contents can not be completely eliminated as possibilities, the lack of conclusive evidence in favor of these factors makes it advisable to remain open-minded concerning the pathogenesis of this lesion. The fact that pulmonary hyaline membranes have been observed in a wide variety of conditions[3-7] serves only to emphasize the need for caution in accepting any one theory, so far as their occurrence in newborn infants is concerned.

The purpose of the present report is to record the occurrence of hyaline membranes, similar in appearance to those seen in newborn infants, in the lungs of vagotomized rabbits and to suggest that perhaps the hyaline membranes in these two species may have a common basis. Farber first reported the occurrence of hyaline membranes in rabbits that had had bilateral midcervical vagotomies, but there is no information available in his report as to the incidence of the membranes, the time of their appearance in relation to the operative procedure or their histochemical structure.[8] The present investigation was undertaken to determine these points and to explore the usefulness of this experimental procedure in studying the pathogenesis of the lesion in lungs of newborn infants.

METHODS

Young rabbits weighing between 1.5 and 2.0 kg. were vagotomized bilaterally in the midcervical region using aseptic precautions and local anesthesia. Efforts were made to determine the hour of death in each rabbit, but this was not always possible. At autopsy a portion of the most involved part of the lung was removed, fixed in 10% formalin and sections were stained with hematoxylin and eosin, Schiff reagent,* Sudan IV, toluidine blue, Gram-Weigert stain, phosphotungstic acid hematoxylin, Masson stain, Perles stain, crystal violet and Verhoeff stain.

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* The Schiff reagent used in this study was the periodic acid, leukofuchsin stain described by McManus[9] and Hotchkiss.[10]

Results

Twenty rabbits were vagotomized and all died spontaneously from 3 to 25 hours postoperatively. Thirteen of the 20 animals were found to have hyaline membranes lining the alveolar spaces of the lungs. Although hyaline membranes were observed in the lung of one rabbit that lived only four hours after vagotomy, they were seen with greater frequency among rabbits with the longer survival periods. As seen in table 1, 9 of the 10 rabbits known to have survived more than 11 hours postoperatively had hyaline membranes, while they were observed in only 4 out of 10 rabbits whose known survival period was 10 hours or less.

TABLE 1

Incidence and Degree of Hyaline Membrane Formation in Lungs of Vagotomized Rabbits According to Length of Postoperative Survival Period

Rabbit No.	Survival Period Hr.	Hyaline Membranes	Rabbit No.	Survival Period Hr.	Hyaline Membranes
31	3	0	25	12–22	2+
40	4	0	36	11–19	3+
41	4	1+	37	11–19	2+
34	7	0	38	11–19	4+
21	7–16	0	39	11–19	4+
22	7–16	1+	32	21	1+
23	7–16	0	28	21	1+
24	8–16	1+	20	22	1+
30	9–16	0	35	25	0
33	10	4+	29	25	3+

The extent to which hyaline membranes were found in any individual rabbit was estimated from microscopic studies of the lungs and was graded from 1+ to 4+. As shown in table 1, there was a tendency for more extensive lesions to be found among rabbits known to have survived more than 10 hours postoperatively.

Pulmonary edema was present in all 20 rabbits, usually to an extensive degree. Hemorrhages into alveoli, polymorphonuclear leukocytic exudate in alveoli and congestion were observed in most of the lungs, but not all. Frequently, these findings were marked. A relationship between the presence and degree of edema, hemorrhage or exudate and the presence of hyaline membranes in the lungs of the rabbits could not be established from these experiments.

The hyaline membranes all stained acidophilic with hematoxylin-eosin. Staining with the Schiff reagent following periodic acid oxidation uniformally showed a pink color in the hyaline membranes of all 13 rabbits, indicating the presence of a polysaccharide aldehyde. The membranes failed to stain metachromatically with toluidine blue. The stains to determine the presense of fibrin, collagenous connective tissue, muscle elements, iron, amyloid and elastic tissue all yielded negative results. In only one animal (rabbit 25) did the membranes show any evidence of sudanophilic material, and this was distributed quite irregularly.

Comment

Microscopic studies of the lungs of vagotomized rabbits are remarkably similar to those of newborn infants who have pulmonary hyaline membranes. Alveolar transudate to some

degree, usually marked, is universally observed in the lungs of both species when hyaline membranes are present. Hemorrhage into the air spaces is less frequent than edema, but is commonly encountered in both. Polymorphonuclear leukocytic exudate in the alveoli and bronchi is also a frequent finding in the lungs of both the rabbits and newborn infants with hyaline membranes. The histochemical findings following the use of special stains are similar. The lungs of newborn infants containing hyaline membranes have been stained in this laboratory—with all the stains employed in the present experiments on vagotomized rabbits—with similar results.[11] So far, a polysaccharide aldehyde is the only substance that has been identified as being uniformly present in the hyaline membranes of both species. Fat evidently is found only occasionally in the hyaline membranes of a rabbit or newborn infant. Fibrin, iron, collagenous connective tissue, amyloid and elastic tissue have not been identified in any of the hyaline membranes of either species. The source of the polysaccharide aldehyde in the membranes of the vagotomized rabbits and newborn infants remains to be determined and is the object of further study in this laboratory. Presumably determination of its source would go far in elucidating the pathogenesis of the membranes themselves.

The time relationship between vagotomy in rabbits and the appearance of hyaline membranes in their lungs is interesting, since it approximates conditions in the newborn infant. In the present investigation as well as in other studies on vagotomized rabbits, hyaline membranes have not been observed in animals surviving less than four hours after the operation—and the severity of the lesion along with the frequency with which it is encountered increase if the rabbits survive more than 10 hours. In a report on a group of consecutively autopsied liveborn infants, the data of Miller and Hamilton show that hyaline membranes were not seen in infants surviving less than an hour after birth and in the group of 28 infants with hyaline membranes the severity of the lesion tended to be greater in the 18 who survived more than 10 hours following birth.[1] This rather surprising similarity suggests that there are perhaps factors which come into operation following the birth of the infant, as in the vagotomized rabbit, which are important in the production of the hyaline membranes. It remains to be determined whether the factors which come into play in the vagotomized rabbits to produce hyaline membranes can in any way be related to the course of events in liveborn infants.

The primary concern of investigators who have experimented with bilateral, midcervical vagotomy in animals has been the pulmonary edema which is universally observed in small animals. This in itself is interesting because pulmonary edema has invariably been encountered in the present authors' studies on the lungs of newborn infants in which hyaline membranes have been present. Edema is not always present in all the alveoli which contain hyaline membranes, but there has not been encountered a lung containing hyalin membranes that did not have edema fluid present in some of the alveolar spaces and usually to a marked degree. Three theories have been advanced as to the cause of pulmonary edema in vagotomized animals:[12] obstructive asphyxia, aspiration of stomach and oral contents, and interruption of neurogenic impulses from reflex centers in the brain. The high incidence of hyaline membranes in vagotomized rabbits suggest that whatever factors are responsible for the pulmonary edema are also concerned with the production of hyaline membranes. There is considerable evidence to support the theory that obstructive asphyxia results from approximation of the vocal cords following midcervical, bilateral vagotomy and that the pulmonary edema is largely dependent on this factor.[13] There is also evidence that the trachea and bronchi readily fill up following vagotomy with material from the

oral cavity.[14] Elimination of both these factors considerably reduces pulmonary edema but does not completely eliminate it[12] and hence has given rise to speculation that some other factor, possibly neurogenic, is also playing a role.

The absence of any conclusive proof supporting the theory of aspirated amniotic sac contents indicates the need for further investigation of the pathogenesis of hyaline membranes in the lungs of newborn infants. The results obtained in vagotomized rabbits suggest additional lines of endeavor. It is not unreasonable to suppose that obstructive breathing can occur in premature infants as a result of collapse of the laryngeal structures, trachea or bronchi on inspiration because of hyperflexibility of these organs. Breathing of this type would be comparable to that occurring in vagotomized rabbits as a result of approximation of the vocal cords. It is also possible that certain premature infants find it difficult to keep the trachea and bronchi free of oral contents, thus again simulating conditions seen in vagotomized rabbits. The matter of a neurogenic component accounting for the changes in lungs of newborn infants with hyaline membranes also lies within the realm of possibility and needs further consideration, particularly since there is considerable evidence that pulmonary edema can be produced experimentally by increased intracranial pressure.[15] The present report has been made not to draw any hard and fast conclusion concerning the pathogenesis of hyaline membranes in newborn infants, but rather to call attention to possibilities that have not as yet received sufficient consideration.

Summary

Pulmonary hyaline membranes similar in appearance to those seen in newborn infants were found in 13 of 20 rabbits vagotomized bilaterally in the midcervical region. The time of appearance of these membranes in relation to the operative procedure in the rabbits approximated closely the time of appearance of the membranes seen in the lungs of newborn infants in respect to the time of birth. In both species a polysaccharide aldehyde was regularly identified in the hyaline membranes. The similarity of the pulmonary lesion seen in vagotomized rabbits to that seen in newborn infants suggests that there may be factors common to both which are responsible for these pulmonary changes.

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SPANISH ABSTRACT

Estudio Comparativo de las Membranas Hialinas Pulmonares Observades en Conejos Vagotomizados y las Encontradas en los Recién Nacidos

Membranas hialinas pulmonares de apariencia similar a las encontradas en los pulmones de los recién nacidos, fueron observadas en trece de veinte conejos vagotomizados bilateralmente en la region cervical. El intervalo transcurrido entre la aparición de las membranas y la operacion de los conejos, se aproximó estrechamente al intervalo existente entre el naciminento y la aparición de las membranas en los pulmones de los niños recién nacidos. Un polisacarido (aldehido) fué identificado regularmente en las membranas de ambas especies. Esta semejanza entre las lesiones pulmonares obtenidas en los animales vagotomizados y las observadas en los recién nacidos, sugiere la posible existencia de factores etiologicos comunes a ambas especies responsables por estas alteraciones pulmonares.

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ACTION OF ALLOXAN ON A HYPOGLYCEMIC INFANT

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SPONTANEOUS hypoglycemia, causing convulsions in infants and children, is very rare.[1] This paper is concerned with a study of an infant who was treated with alloxan for severe spontaneous hypoglycemia and associated convulsions.

CASE PRESENTATION

An 8 mo. old white female infant was admitted to the Children's Hospital, State University of Iowa, with the chief complaint of convulsions during the past 6 wk.

The family history and past medical history were noncontributory, with the possible exception that vitamin D and C supplements had been given sporadically. During the period of hospitalization a sibling was born, and has been under observation the past year. This sister's blood sugar values and glucose tolerance tests are normal.

The patient's illness began 1 mo. before admission when she had a generalized convulsion lasting 60 min. She was then asymptomatic for 11 days when she had attacks of a similar nature. She was hospitalized locally for observation and study. During her hospitalization there was no evidence of infection. The cerebrospinal fluid was reported to be normal. Chemical analysis of the blood revealed normal values for calcium, phosphorus and phosphatase. Calcium therapy did not control the convulsions. The attacks were initiated by a shrill cry and followed by a generalized clonic, tonic convulsion and occurred 3 to 4 times a day. Convulsions appeared at various times during the day regardless of feeding schedule. The child was referred to the State University of Iowa for further observation and study. The physical examination on admission disclosed an obese female infant of short stature (see chart 1; the body contour was similar to Fig. 1A). Her temperature, and pulse and respiration rates were normal. She was lying on her back, unconscious, flaccid, showing no response to painful stimulation. Within a period of 1½ hr., however, the child gradually responded to stimuli, became conscious, active and played normally. The physical examination at this time revealed nothing abnormal. Furthermore, initial laboratory studies showed the following to be normal: hemogram, CO_2 combining power, NPN, total serum protein, calcium, phosphorus, phosphatase and Wassermann test. However, the blood sugar value obtained by a micromodification of the Folin-Wu for estimation of sugar content and the Somogyi method of precipitation was 16 mg./100 cc. and the cephalin flocculation was 4+ in 48 hr.† The diagnosis of hypoglycemia was made.

An attempt was made to control the hypoglycemia by medical management. A whole milk formula with a protein hydrolysate supplement was given but the patient continued to have 3 to 4 convulsive attacks each day. On the 19th hospital day she was given intramuscular injections of 0.37 cc. of 1/500 solution of adrenalin in oil, 3 times a day. With this therapy, the convulsive attacks became milder and did not lead to unconsciousness, but the irritability, tremors and hypoglycemia persisted. Her glucose tolerance curve was practically level (chart 2, #1).

At this time, urine examinations revealed normal values for creatinine, uric acid, 17-ketosteroids and NPN, and no albumin, reducing substance, acetone or abnormal microscopic findings. Blood amino-nitrogen levels were normal. Roentgenograms of the skull, chest and gastrointestinal tract

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† The chemical determinations were made in the Pediatric Research Laboratory through the courtesy of Dr. G. Stearns.

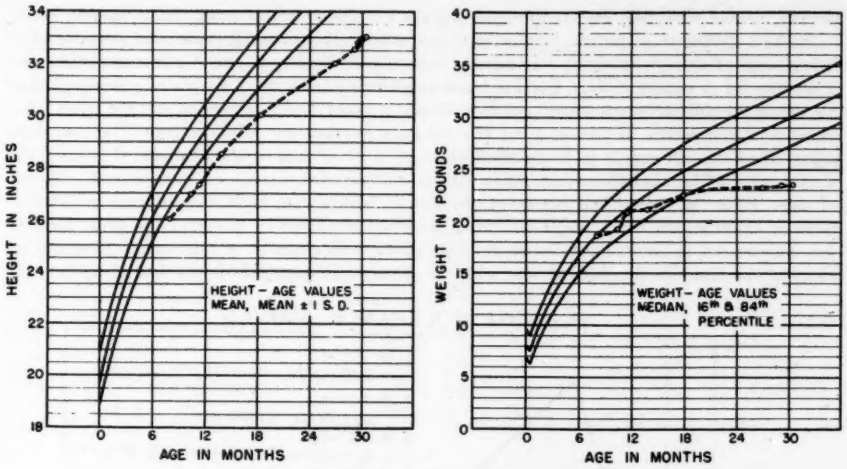

CHART 1. Broken line represents height and weight values of patient during period of study in relation to Iowa Standards.

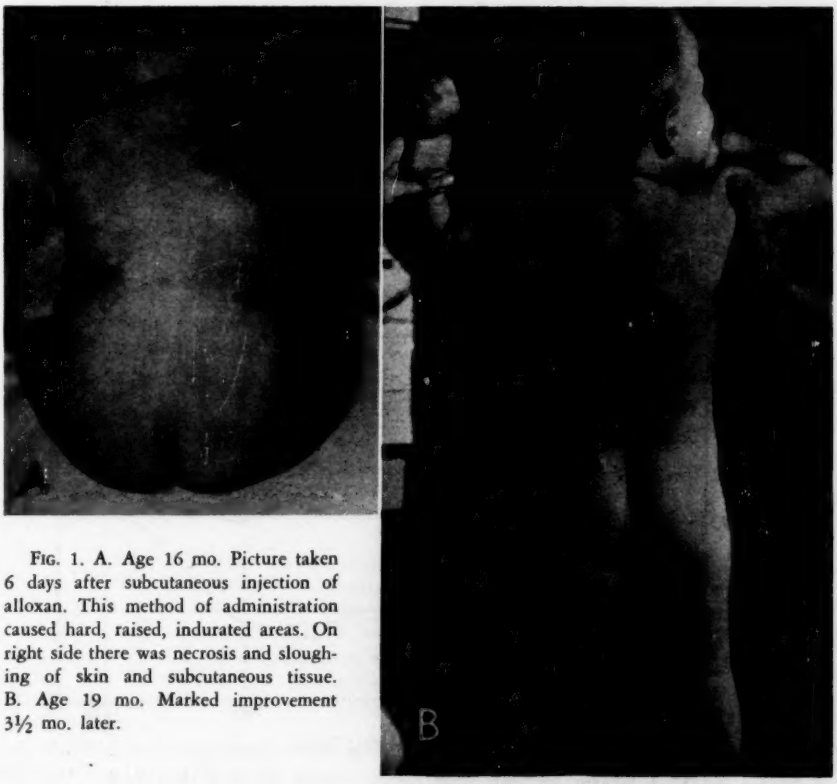

FIG. 1. A. Age 16 mo. Picture taken 6 days after subcutaneous injection of alloxan. This method of administration caused hard, raised, indurated areas. On right side there was necrosis and sloughing of skin and subcutaneous tissue. B. Age 19 mo. Marked improvement 3½ mo. later.

showed nothing abnormal. An electroencephalogram was interpreted as being within normal limits.

Several additional diagnostic studies were performed. The patient's urine was assayed for a hypoglycemic factor. A specimen was injected intraperitoneally into 6 rats, 3 adrenalectomized and 3 normal, for 2 successive days, but the blood sugar levels from the 2 groups of animals showed no significant differences. A slight elevation in blood sugar levels of the infant was noted after intramuscular injections of adrenalin but this elevation persisted for only 4 to 6 hr. The low blood sugar values did not appear to be modified when 35 cc. of adrenal cortical hormone (Upjohn) was given over a 24 hr. period or when .03 to .06 gm. of desiccated thyroid was administered daily for 15 days. From the clinical and laboratory observations which were made there was no evidence of pituitary hypofunction which might lead to an increased sensitivity to insulin. Thus, great difficulty was encountered in determining the exact cause of the hypoglycemia in this infant. After having observed the child in the hospital and with the information gained from the special studies just

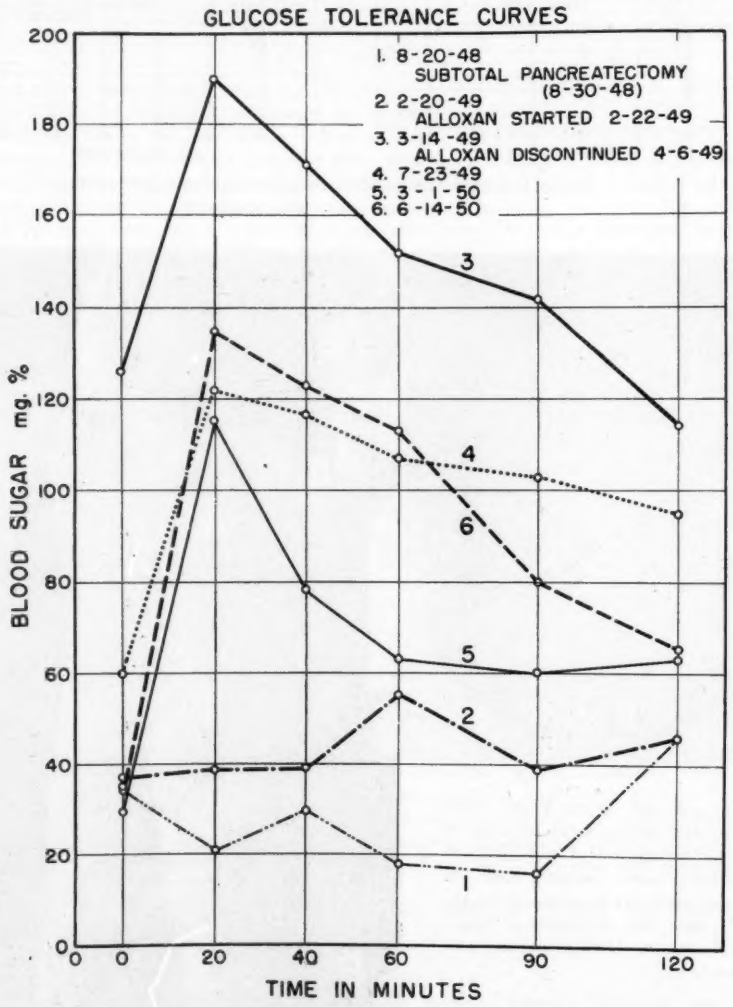

CHART 2. Glucose tolerance curves obtained during period of observation.

TABLE 1

Date	Remarks	Blood sugar values* mg./100 cc.			Alloxan Therapy Alloxan given as 5% solution made up in saline or distilled water	
		Low	High	Ave.	mg./kg.	
8/6/48	1st admission	16	—	—		
8/9		16	—	—		
8/11		14	25	18		
8/15	Taken during attack	9	76	—		
8/20		16	46	27		
8/25		9	41	19		
8/28		0	11	6		
8/29		11	34	26		
8/31	Post pancreatectomy	138	311	204		
9/1 to 9/7		74	114	87		
9/8 to 9/18		51	69	57		
1/19/49	2nd admission	14	28	22		
1/20		9	40	26		
1/26		9	122	53		
1/28		28	—	—		
2/5 to 2/21/49	3rd admission	3	51	37		
2/22 to 3/6	Alloxan given 15 days	0	97	55	25–55	Diluted in 100 cc. saline†
3/7 to 3/14	Alloxan given 5 days	29	172	68	55–60	Diluted in 100 cc. saline‡
3/15 to 3/21	No alloxan	27	93	60		
3/22 to 4/6	Alloxan given 7 days	29	125	66	50–75	No dilution‡
4/3 to 4/6	Alloxan given 3 days				150	Diluted in 225 cc. saline§
5/16/49	Fasting	63	—	—		
6/13	Fasting	73	—	—		
7/20	Fasting	75	—	—		
7/27	Fasting and semifasting	53	85	71		
9/6	Fasting	70	—	—		
10/12	Fasting	35	—	—		
3/1/50	Fasting and semifasting	30	115	68		
5/4/50	Fasting and semifasting	45	73	55		
6/14	Fasting and semifasting	35	135	92		

* Normal fasting levels 60 to 80 mg./100 cc.

† Alloxan was given intravenously by slow drip over 1 hr. period.

‡ Alloxan was given intravenously by rapid injection over a period of 1 min.

§ Alloxan was given subcutaneously but slowly over period of 2 hr.

reported, several possibilities remained. The patient might have a true hyperinsulinism, caused either by an islet cell tumor or by a hypertrophy of the islets of Langerhans; or a relative hyperinsulinism, caused by an atrophy of the alpha cells of the islets.

Surgical consultation was obtained. It was the consensus of both the pediatric and surgical departments that since medical management was not causing appreciable improvement in the hypoglycemic state, more radical procedures would have to be employed. It was decided, therefore, to explore the abdomen of the child and if a pancreatic tumor was not found, a subtotal pancreatectomy was to be done.

Twenty-four days after admission the abdomen was explored and found to be normal in every respect. About 90 to 95% of the pancreas was removed together with the spleen and a piece of

liver was removed for biopsy. The liver specimen contained 2.7% glycogen which value was higher than normally found.

Glycosuria was present 24 hr. after the pancreatectomy and blood sugar values remained elevated for a period of 10 days (table 1). During the next 3 wk. the blood sugar dropped to low normal levels. However, the child had no further convulsions and was sent home 1½ mo. after operation. Her diet consisted of the usual solid foods for a 1 yr. old child and a whole milk formula with 7% carbohydrate added, divided into 6 equal meals.

The patient was followed in the outpatient clinic and remained well for 3 mo. She was re-admitted 3 mo. after discharge because of irritability, food refusal and generalized convulsions. The physical examination revealed a 13½ mo. old child whose developmental level was estimated to be that of 10½ mo. Her blood sugar was 28 mg./100 cc. and she had a low glucose tolerance curve (chart 2, #2). Laboratory studies showed a positive nitrogen balance. An EEG was abnormally slow when the patient was awake, and while asleep showed low voltage spikes, which were possibly lateralized. Because of the low blood sugar levels and severe convulsions, it was obvious that the subtotal pancreatectomy had only temporarily aided the child and that further therapy was indicated. At this time she was receiving intramuscular injections of 0.37 cc. of 1/500 solution of adrenalin in oil, 3 times a day.

On the 34th day treatment with intravenous injections of alloxan monohydrate was instituted and continued daily for 20 days. Initially she was given 25 mg./kg. body weight but this was increased to 60 mg./kg. by the end of this injection period (see table 1). Seventeen hundredths milliliter of a 1/500 solution of adrenal in oil was given 3 times a day during the 1st 15 days of alloxan treatment. The intravenous injection of alloxan produced no untoward systemic effects but it proved to be a remarkable sclerosing agent. Once a vein was entered it was generally impossible to re-enter it for another injection.

The child had no convulsions during the 20 days she was receiving alloxan and remained well for 5 days after this treatment. Her glucose tolerance curves were markedly improved (chart 2, #3) and semifasting blood sugar values were somewhat higher (table 1). However, on the sixth and again on the ninth day after alloxan was discontinued, she had severe generalized convulsions. Consequently, a second course of alloxan treatment was started immediately. The dosage was eventually increased to 75 mg./kg. body weight. Seventeen hundredths milliliter of the adrenalin solution also was given twice daily as a safeguard against severe convulsions. After 8 days of treatment there was no definite improvement in her blood sugar values and all available veins which could be used were sclerosed. As a final attempt, large doses of alloxan (150 mg./kg. body weight as a 0.6% solution) were given for 3 days by the subcutaneous route. This method of administration proved painful, the fluid was absorbed slowly and produced hard indurated areas that eventually broke down (Fig. 1 A and B).

The clinical course after alloxan treatment was uneventful. The child was sent home from the hospital 2 wk. after the last injection of alloxan, receiving 1400 calories divided into 7 meals a day and .17 cc. of 1/500 adrenalin in oil twice daily. Within 1 wk. the mother discontinued the adrenalin and was giving the child only 4 meals a day. The patient was observed in the outpatient clinic 9 times during a 14 mo. period. She remained well and free from convulsive attacks. The blood sugar values showed improvement although some values were low (table 1) and the glucose tolerance curves, although not entirely normal, also showed improvement over the picture seen before the alloxan treatment (chart 2, #4, 5, 6). These findings may be explained partly in that her diet had been higher in carbohydrate than recommended. Other laboratory studies, similar to those carried out at the time the patient was first admitted to the hospital, showed values within the normal range. The cephalin-flocculation test was recorded as ± in 48 hr. On the last admission, the patient's height and bone age were retarded 6 to 9 mo., but her social developmental age was within normal range. Recent EEGs indicated that there may be some deep cerebral damage on the right side. From the routine studies which were made, there has been no evidence that the alloxan treatment produced liver or kidney damage in this patient.

Histologic Study of the Pancreas

The surgical specimen of the pancreas, obtained at the time of the subtotal pancreatectomy, was studied carefully in an attempt to ascertain the cause of the hypoglycemia. Unfortunately, the specimen was not preserved adequately for a detailed cyto-

logic examination. The islets were large and numerous but this is typical for the pancreas of such a young child. Using Gomori's aldehydefuchsin trichrome stain,[2] however, it was observed that only a few of the beta cells were normally granulated and the alpha cells appeared autolyzed.

Because of the assumption that the alpha cells probably produce a hyperglycemic factor in the pancreas,[3] it was thought that the examination of the islets might give some clue as to the cause of the hypoglycemia. That is, if the hyperglycemic substance were decreased in amount, it would require much less of the insular hypoglycemic factor to cause the severe hypoglycemic state. Because the alpha cells appeared autolyzed, in the present specimen, it was possible only to conclude that the beta cell picture was not incompatible with the presence of extrapancreatic insulin secreting tissue elsewhere in the body.

Discussion

Hypoglycemia in infancy and childhood is uncommon and when encountered is ordinarily mild, responding readily to adrenalin or intravenous glucose, and is controlled by dietary management. In the case reported, such management failed to elevate appreciably the blood sugar levels or allay the convulsive seizures. A subtotal pancreatectomy also failed to sustain normal blood sugar values. It therefore became necessary to employ more radical procedures to prevent progressive cerebral damage and death.

Three therapeutic agents, alloxan monohydrate, cortisone and ACTH were considered for further treatment, but each had distinct disadvantages. The two hormones were not available for therapeutic trial. According to recent reports in the literature,[4,5] either of the two hormones should have improved the hypoglycemic state; however, it has been found necessary to continue administration of the drugs more or less indefinitely to maintain control of the disease. Alloxan had been used previously by Talbot et al.[6] to treat an eight month old infant with severe convulsions due to an idiopathic hypoglycemia. Although this drug was apparently responsible for the elevation of the blood sugar values in their patient, the authors warned that the drug was potentially dangerous. The present authors realized that although alloxan might alleviate the convulsions and elevate blood sugar values, there was the possibility that this chemical might produce a mild diabetes which would become more severe as the child grew older. Furthermore, Brunschwig and Allen[7] found that alloxan caused a necrosis of the beta cells of the islets in an adult human, but believed that in addition to this action, the drug caused degenerative changes in the liver and kidneys. Consequently there was a great deal of reluctance in giving alloxan.

Even with the many contraindications, it was decided to treat the infant with alloxan in a further attempt to raise her blood sugar levels. Great caution was exercised when alloxan therapy was started. The initial dosage of 25 mg./kg. body weight, given by slow intravenous drip, curtailed her convulsions, but real improvement in blood sugar levels and glucose tolerance did not appear until 60 mg./kg. body weight was given by rapid intravenous injections. During the 30 days in which alloxan was given, she received a total of 1750 mg./kg. body weight. While small amounts of adrenalin were given simultaneously with the alloxan injections, it is the opinion of the authors that the alloxan produced the sustained improvement in this patient. Fourteen months after the alloxan therapy was discontinued, the child was still free of convulsions and there was a decided improvement in the glucose tolerance curves although some of the observed blood sugar values were low.

The response noted in this child with alloxan therapy indicates that the initial dose should be approximately 55 mg./kg. body weight, given by rapid intravenous injection. The dose should be increased by 5 mg./kg. daily until a mild hyperglycemia is produced.

Summary

A case report is presented of an eight month old white female who had a severe spontaneous hypoglycemia with associated convulsions. This condition was not appreciably improved with medical management and a subtotal pancreatectomy gave only temporary relief. The administration of alloxan monohydrate caused a cessation of convulsions, elevated the blood sugar and improved the glucose tolerance. The response noted in this child with alloxan therapy indicates that the initial dose should be approximately 55 mg./kg. body weight given by rapid intravenous injection. The dose should be increased by 5 mg./kg. body weight daily until a mild hyperglycemia is produced. Fourteen months after the last injection of alloxan the child had remained free of convulsions and her social developmental age was considered to be within normal limits. Blood sugar values obtained during the 14 month interval were improved over the pre-alloxan picture. However, values below the normal fasting level have been observed.

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Spanish Abstract

Acción del Alloxan en un Niño Hipoglicemico

Los autores describen un caso de una niña de ocho meses de edad, blanca, con una hipoglicemia espontánea severa, asociada con convulsiones.

No se obtuvo mejoria con el tratamiento médico y la pancreatectomia subtotal solo produjo una mejoria transitoria. La administración de monohidrato de alloxan resultó en la cesación de las convulsiones, en un aumento de la glucosa sanguinea y una mejoria en la tolerancia a la glucosa. Basándose en los efectos producidos en este paciente, los autores sugieren que la dosis de alloxan debe ser aproximadamente de 55 miligramos por kilogramo de peso administrada mediante una inyección intravenosa rápida. La dosis de alloxan debe aumentarse diariamente 5 miligramos por kilogramo de peso hasta que una hiperglicemia benigna sea producida. El paciente presentado ha permanecido libre de convulsiones durante un periodo de catorce meses siguientes a la última inyección de alloxan, y su desenvolvimiento social fué considerado entre los limites normales. Los valores de la glucosa sanguinea obtenido durante ese intervalo estaban por encima a los obtenidos en el periodo pre-alloxan. Sin embargo, en ocasiones valores subnormales en ayunas han sido observados en este paciente.

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RELATION OF O_2 CONSUMPTION TO CIRCULATION IN DIFFERENT STAGES OF INFANTILE MALNUTRITION

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IT WAS found in a previous study[1] that circulation is seriously impaired in severe infantile malnutrition. This fact led to an inquiry as to how far the diminished circulation satisfies the metabolic needs of the malnourished infant.

In this endeavour oxygen consumption, circulation time, cardiac output and the arterio-venous O_2-difference were determined simultaneously in groups of undernourished infants.

METHODS

The malnourished infants were divided, according to the gravity of their clinical condition, into 3 groups. The first group covers cases of severe "dystrophy," the second those of severe "atrophy" and the third, cases of "athrepsia" ("decomposition"). The classification was made according to the classical descriptions of Finkelstein[2] and Marfan.[3] The average age of the infants was the following: normals, 4 mo.; dystrophia group, 5.5 mo.; atrophia, 3.5 mo.; athrepsia, 3 mo. The severely "dystrophic" group was 31%, the "atrophic" and "athreptic" groups 40% underweight.

O_2 consumption was determined according to Kestner[4] and Schadow[5] in experimental periods of 1 hr. duration. Circulation time was measured with Congo red dye.[1] Oxygen in the blood was measured according to Van Slyke.[6] An estimate of cardiac output was attempted, using a modification of the Fick principle: (cardiac output $= \frac{O_2 \text{ consumption}}{\text{arterior-venous } O_2}$). The difficulty of applying this method in infancy lies in obtaining the O_2 content of mixed venous blood. Catheterization of the right heart in badly ailing infants presents some dangers. In the calculations, therefore, the present authors have used the O_2 content of cerebral venous blood obtained by puncturing the sinus longitudinalis. On the basis of the data which follow it is felt that this modification, however open to criticism, does not significantly alter the results: 1. The O_2 content of sinus blood in normals is remarkably constant, and only slightly lower than mixed venous blood.[7,8] 2. In 2 normal infants cardiac output was only about 10% lower when calculated from cerebral venous blood instead of mixed venous blood. 3. In 2 dehydrated infants cardiac output values, calculated from sinus, or from heart blood, showed a fairly good agreement.[8] 4. Changes in cardiac output and in circulation time, as will be seen from the data, show a close agreement in all normal and pathologic cases.

EXPERIMENTAL DATA

All the data are summarized in chart 1.

The height of the columns represent the O_2 transported to the tissues per minute (i.e., cardiac output x vol. % of arterial O_2). The blackened portion of the column represents O_2 consumption. All values are calculated to a surface area of 1.73 m^2. Individual values are represented by circles; the columns show the mean values. The mean values for the arterio-venous O_2 difference and circulation time can be read at the top of each column. In the normal infant O_2 transport is double the amount consumed. In the adult O_2 transport is higher, in view of the higher blood hemoglobin (and blood O_2) content and somewhat larger cardiac output. In the severely dystrophic group O_2 consumption is

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somewhat higher and so is O_2 transport. Circulation time and arterio-venous O_2 difference are unchanged. It is a well established fact that basal metabolism generally rises in malnutrition, especially if calculated/kg. actual weight.[9-11] The increase, as is shown in this chart, is still apparent when basal metabolism is related to body surface. In clinically more severe forms of malnutrition metabolism appears, however, to be "normal" or even decreased.[12,13] The data reveal that in progressively severer stages grave disturbances set in, affecting both oxygen consumption and circulation. In severe atrophy O_2 consumption decreases, so does O_2 transport, the diminution in transport, however, being somewhat greater. In athrepsia O_2 transport is dangerously close to O_2 consumption, the arterio-venous O_2 difference is broadened, circulation time doubled. Thus, while in atrophia

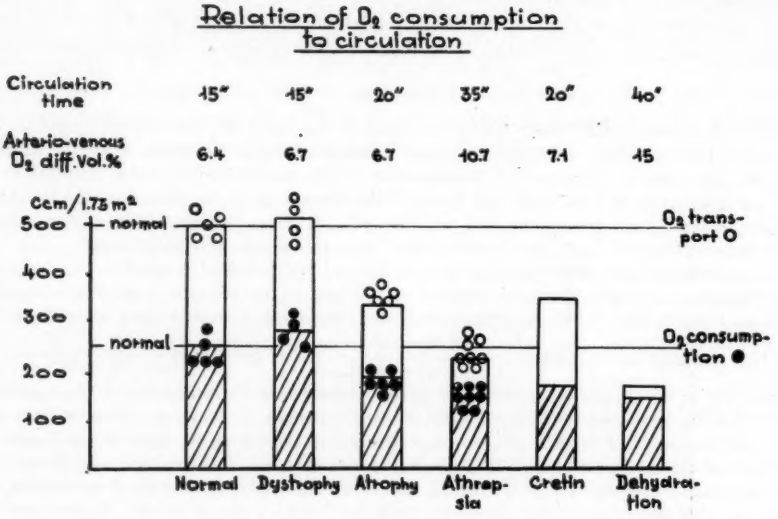

CHART 1

circulation is more or less adjusted to decreased metabolic needs, in athrepsia circulation collapses far below the metabolic needs of the wasted body. There appears, superimposed upon the slowing up of circulation characteristic of severe atrophia, a real failure of circulation, involving a condition of anoxia of the stagnating type.

The significance of these changed relations between O_2 supply and consumption in wasting can be better understood when compared with other conditions involving decreased O_2 consumption. The last two columns show conditions found in hypothyreosis and in severe dehydration. In the case of a cretin 2 years of age of the size of a young infant, decrease in O_2 consumption was paralleled by an approximately equal decrease in circulation. Slowing of circulation (i.e., decrease in cardiac output) seems to be adjusted to the smaller call of the tissues for O_2. The similarity to atrophia is striking. This is not so in severe dehydration. Serious circulatory shock is evidenced by the fact that the margin between O_2 transport and consumption almost completely disappears; the arterio-venous O_2 difference is enormously broadened, circulation is very slow. Thus, low O_2 consumption is clearly secondary to primary failure of circulation. Tissues of normal O_2 requirement are inadequately supplied with O_2, owing to circulatory shock. Even

maximal utilisation of each cubic centimeter of O_2 transported to the tissues is insufficient to bring about a normal consumption. A state of severe stagnating anoxia is created, involving "toxic" symptoms: loss of consciousness and acidosis.[7,8]

Returning now to athrepsia, low O_2 consumption is clearly the result of two processes: 1. The metabolic need of the tissues has diminished during the preceding long process of "atrophy" and inanition. 2. Circulatory failure adds its effect to the former process by further decreasing O_2 consumption. In spite of very low O_2 consumption and circulatory failure, the athreptic infant is less anoxic and "toxic" than the dehydrated one, because its metabolic need is slighter.

Comment

An analysis of the mechanism leading to the slowing of circulation in severe malnutrition is not the purpose of this paper. The same facts were observed in wasting starving adults by Govaerts[14] and in the famous Minnesota experiments.[15] The heart is certainly wasted in all marantic conditions;[1,15] electrocardiographic changes were described in adults and infants.[16] But in the terminal stage of malnutrition, athrepsia, there is more than an adjustment of circulation to lowered metabolism; the rapid deterioration of circulation is clearly connected with hemoconcentration; plasma volume decreases, the red count and hematocrit increase.[17] Rapid weight-loss is known to be characteristic of this condition.[2,3] Clinically, the high mortality of marantic infants in intercurrent infections appears connected with poor circulation. Intercurrent pneumonia, by lowering arterial O_2 capacity, will add its effects of "anoxic" anoxia to those of the "stagnating" anoxia characteristic of the athreptic condition. Diarrhea leading to dehydration will rapidly cause deterioration of the precarious circulation and increase pre-existing stagnating anoxia. It is thus comprehensible that intercurrent infections, in spite of ample use of antibiotics, lead to high mortality rates in severely wasted infants.[17]

Summary

The relation of O_2 consumption to circulation was studied in varying stages of infantile malnutrition. In severe "dystrophy" O_2 consumption and circulation are somewhat increased. In severe "atrophy" both cardiac output and O_2 consumption fall to lower values, the lowered metabolic need of the tissues, however, being met by even a slower circulation. The condition is similar to that found in hypothyreotic patients. In athrepsia circulation collapses far below the metabolic need of the wasted organism; anoxia of the stagnating type ensues. Anoxia is, however, milder than in severe anhydremic circulatory shock, because the metabolic need of the tissues has decreased during the long atrophic and inanition period that preceded the terminal, athreptic stage of malnutrition. The poor circulation of the severely marantic infant may be an important factor in the high mortality rate when such patients suffer intercurrent infections, especially in pneumonia and diarrheal disease.

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SPANISH ABSTRACT

Estudio del Consumo de Oxigeno en Relación la Circulación en Diferentes Grados de Desnutrición

El consumo de oxigeno en relación a la circulación fué estudiado en estados variables de desnutrición. El consumo de oxigeno y la circulación estuvieron aumentado en las distrofias severas. En las atrofias severas, tanto el volumen cardiaco como el consumo de oxigeno disminuyeron a valores mas bajos, sin embargo, las necesidades metabolicas de los tejidos fueron llenadas gracias a una circulación aún mas lenta. Un estado similar es encontrado en los pacientes hipotiroideos. En los estados atrepsicos las necesidades metabolicas del organismo desnutrido no pueden llenarse debido al colapso circulatorio, lo que da lugar al desarrollo de una anoxemia. Esta anoxia es menos severa que la observada en el shock circulatorio anhidremico, debido a que las necesidades metabolicas están disminuidas durante los periodos prolongados de atrofia y inanición que anteceden la fase final o atreptica de la desnutrición. Se estima que la circulacion deficiente de los niños con marasmo severo puede ser un factor importante en la alta mortalidad observada en estos pacientes cuando desarrollan infecciones intercurrentes, especialmente pneumonias y diarreas.

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OMPHALOCELE

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OMPHALOCELE is one of the rarer conditions encountered in the field of general surgery. It has been estimated to occur in from 1 in 5,000 to 1 in 10,000 births. The term "omphalocele," first suggested in 1940 by Gross and Blodgett,[1] applies to umbilical herniation in the newborn infant in which a portion of the sac is composed only of peritoneum and glistening amniotic membrane through which the intestinal contents may be clearly seen. It should not be confused with the common umbilical hernia, in which the sac is much smaller and is always completely covered by skin. Omphalocele is generally conceded to be caused by a failure of the intestines to return to the abdominal cavity from their temporary developmental position in the umbilical cord.

Omphalocele, as brought out by Jarcho,[2] has been known from the time of Celsus, and also described by Ambrose Paré in 1640. In early times, all babies were treated conservatively and nearly all died due to ultimate desiccation of the sac, followed by rupture of the membrane and peritonitis. From 1900 to 1920, surgical treatment gained in favor and many were successfully operated upon. Mortality continued to be high because of delay, poor technic and ignorance of the physiologic requirements of the membrane.

Since Jarcho's excellent review in 1937, isolated case reports or small series of cases have been published by Maguire,[3] Ferguson,[4] Kern[5] and Adams,[6] so that discussion of the subject in detail is not necessary here. It is believed that the tone of the last three reports in American literature, those by Gross,[7] Maguire and Adams, should change completely the attitude of the surgeon towards this condition, so that any given case of omphalocele uncomplicated by unrelated, ultimately fatal congenital anomalies should result in a favorable outcome in a high percentage of cases operated upon. The newborn infant, with an umbilical mass which may be larger than the abdomen and may contain all the mobile viscera including the liver, must be transferred directly from the delivery table to the operating table, if a successful outcome is to be assured.

In Gross' and Blodgett's series of 22 cases reported in 1940, the mortality was less than 50%, due mainly to the prevention of the major cause of death—that of peritonitis as a result of disintegration of the serous sac. They also suggested a modification in surgical technic to help overcome the second main cause of death—that of respiratory and cardiac embarrassment due to overcrowding of the abdominal cavity. They recommended that in cases where large sacs with large defects in the abdominal wall were found, the skin alone should be drawn over the protruding intestines after resection of the sac.

This general idea was carried further by Gross in 1948. He uses and recommends a form of treatment that interferes to a minimum with physiologic functions, namely, a

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two-stage repair of the defect. The first stage consists of encircling the glistening sac by an incision, undermining the skin of the abdomen and bringing it together over the protruding mass without opening the sac. The second-stage repair of the hernia at a later time when the abdominal wall has enlarged is a relatively simple procedure. This last refinement in technic promises to lower the mortality in this condition to that of other major surgical procedures.

There have been but two cases reported in which recovery has occurred when the child was born without a sac; that is, rupture of this structure having occurred prior to or during labor and the intestines found lying free on the abdominal wall. Adams, in the March 1948 issue of the *Journal of Pediatrics,* was the first to report a cure when these conditions were present. Maguire in the *Annals of Surgery,* September 1949, also treated such a patient successfully. The successful outcome in their cases and in the one to be reported, where peritonitis was already present, was undoubtedly due to modern chemo- and antibiotic therapy which in former years was unavailable. Also, much has been learned of the physiologic needs of the newborn infant; it is now possible to keep infants alive and in good nutritional and electrolyte balance for many days by parenteral and intravenous therapy. The following case report was felt to be of sufficient interest to justify reporting.

Case Report

Baby F. was born at full term at 6:00 p.m. on March 4, 1949. Labor was not difficult and was assisted by episiotomy and outlet forceps. The child at birth was apparently well developed, full term, vigorous, and weighed 2.6 kg. The only pathologic finding was the protrusion of the entire small bowel and colon, from the ligament of Treitz to the rectosigmoid, from an outlet at the umbilicus, which was approximately 4 cm. in diameter. The bowel, which was almost the consistency of cartilage, was covered with a fibrinous purulent-appearing exudate. There was no suggestion of a lumen. It was impossible to differentiate the small bowel from the colon even after close inspection. There was no sac covering the viscera. The large vessels of the cord entered in the right lateral aspect of the defect in the abdominal wall. This defect was drawn tightly around the mesentery of the bowel and, no doubt, was the cause of the strangulation, edema and discoloration of the viscera. They were beefy red and looked as if they were gangrenous. The cord was quickly tied, the bowel covered with sterile gauze saturated with saline, and the child was moved immediately to the operating room and prepared for surgery in the usual manner. The anesthetic employed was sugar and whiskey administered through a small gauze nipple.

First inspection of the bowel on the operating table led to the conclusion that there was an actual agenesis of part of the bowel (Fig. 1). The protuberance toward the midline was interpreted as being the terminal end of the small gut, and that on the lateral side was interpreted as being the edematous appendix. There seemed to be no bowel in between these two points. Since resection would mean the removal of the entire bowel, from the ligament of Treitz to the rectosigmoid, and anastomosis was impossible, it was felt that the child's condition was hopeless.

In order to return the bowel into the abdominal cavity, it was necessary to extend the abdominal opening for a distance of about 3 cm. proximal and distal to the umbilicus. After the bowel was thoroughly irrigated with saline, it was replaced. The abdominal wall was extremely tense, and it was impossible to close the fascia for a distance of approximately 8 cm. However, the skin was undermined after removing the entire remnant of the umbilical cord, so that it alone could be brought over the viscera; 4-0 and 5-0 silk were used in the repair (Fig. 2). The skin was closed with the same suture material, a Wangensteen tube was inserted into the stomach, and the infant was sent to the nursery with a hopeless prognosis.

Continuous Wangensteen suction was maintained for 3 days and intermittently for 2 additional days. Oxygen by funnel was begun and aqueous procaine penicillin 400,000 units and streptomycin ¼ gm. were given intramuscularly daily. Clysis of 30 cc. of 5% glucose in lactate Ringer's solution was administered twice daily. Oxygen was continued intermittently for 1 mo. because of

FIGS. 1-3. Baby F. Arrows point to apparent blind ends of bowel, felt at first to be actual agenesis. Protuberance on left later interpreted as Meckel's diverticulum; that on right as edematous appendix. 2. Bulging abdomen resulting from closure of undermined skin over bowel protruding through unsutured fascia layer. 3. Child following operation is well nourished with no evidence of hernia. Asymmetry of abdomen is due entirely to child's position.

cyanotic attacks, probably due to abdominal distention and bronchial obstruction caused by thick mucus. The penicillin and streptomycin were discontinued in 1 wk., but clysis was continued in varying amounts for 9 wk.

By the third postoperative day, the rectal temperature had gone up to 40.0° C., no meconium had been passed, but adequate voidings had occurred. The abdomen was distended and hard, respirations were labored and the infant, although not dehydrated, seemed in poor condition. The Wangensteen tube became clogged with thick mucus several times and had to be cleaned and reinserted. One ounce of water every 2 hr. was started by gavage via the Wangensteen tube.

On the fourth postoperative day, a small amount of semiliquid dark green meconium and a

large amount of flatus were passed per rectum, and the abdomen became soft. Later in the day, a considerable amount of green liquid and mucus was regurgitated. The temperature was normal and the general condition seemed somewhat improved.

It might be mentioned at this time that the obstetrician, Dr. H. E. Bowles, was certain that meconium was present in the amniotic fluid. In view of the apparent operative finding of agenesis of the bowel, it was difficult to account for this. However, on the fourth day when the child began to pass gas and meconium, it was realized that the original concept was incorrect and there must be some other explanation for the peculiar configuration of the bowel found at surgery. What was felt at the time of operation to be the end of the terminal ileum was now believed to be a Meckel's diverticulum; the short distance in which the bowel appeared to be absent could only be interpreted as the small portion of the terminal ileum that is often retroperitoneal; and the other small nubbin of tissue must have been the edematous appendix. According to Ferguson and others, a Meckel's diverticulum often accompanies omphalocele, as do other congenital anomalies.

On the fifth postoperative day, again a small amount of green meconium and mucus was passed per rectum. Olac® (1 tablespoon to 2 oz. of water), 1 oz. every 2 hr., was started. The next day, the Wangensteen tube was withdrawn because the extreme distention had subsided. There had been 3 small green stools, and although the regurgitation of green fluid and mucus and formula occurred several times, the child probably retained about one third of the feedings. This amount of daily regurgitation continued unabated for about 3 wk., then gradually decreased. Blood transfusions of 60 cc. were given repeatedly as supportive treatment. The infant's weight at the end of 1 wk. was 2.5 kg., the same as on the second day, and 170 gm. more than on the fifth day.

During the next 10 days, the stools continued to be green and scanty and to contain what appeared to be flecks of milk curds. Moderate distention was usually present and marked abdominal distention occurred several times. Regurgitation continued as before. The weight and blood count remained the same. Daily clysis of 60 cc. of lactate Ringer's solution was administered, and about 14 oz. of olac® (2 tablespoons/3 oz. water) were taken fairly well in 1½ to 2 oz. feedings. Mild cyanosis was present most of the time in spite of continuous oxygen.

No improvement in the condition seemed apparent so the clysis was increased to 160 cc. daily. Crysticillin, 100,000 u. daily, was started again and zymadrope® (vitamin mixture) 5 minims and Karo (1 oz./8 oz.) were added to the formula. A 60 cc. blood transfusion was given and repeated again in 3 days.

A gastrointestinal series at this time (3 wk.) was reported as follows: "Preliminary film of the abdomen shows a considerable amount of gas in the intestinal tract greatly obstructing the visceral detail. No significant abnormality noted. Examination of the gastrointestinal tract shows the stomach to be slightly dilated. No barium passed into the duodenum during fluoroscopic examination. Films made at 1, 2, 4 and 24 hour periods show a definite delay in the emptying of stomach at 24 hours. There is still a considerable amount of gastric residue. No point of organic obstruction can be made out. The cause of delay is not definitely known. Several small intestinal segments appear to be mildly dilated. There is very little barium in the colon even at the 24 hour period. Advised a 48 hour film. Examination at 48 hour period still shows a considerable amount of gastric residue, further indicating some sort of obstruction in the distal portion of the stomach or duodenum."

On the twenty-second postoperative day, the infant's condition seemed grave. The abdomen was markedly distended and vomiting had increased. The Wangensteen suction was again started; a neoprene tube was inserted in an arm vein and 450 cc. of 5% glucose in lactate Ringer's solution was given slowly by continuous drip, through a polyethylene tube, over a 48 hr. period. The same solution and amount plus acids (parenamine®) 100 cc. was given during the next 48 hr.

The child's condition then improved markedly and continued to improve gradually for the next 7 wk. when he was discharged on the seventy-fifth hospital day, on a normal diet and weighing 3.7 kg. It was believed by all observers that the continuous intravenous drip given at this critical period was life-saving.

Following the crisis at the end of the third week, essenamine® (3 oz.) added to each day's formula apparently reduced the frequency of vomiting and increased the rate of weight gain.

The abdominal incision healed by first intention, and the sutures were removed on approximately the seventh hospital day. Surprisingly, no hernia of the abdominal wall had or has occurred (Fig. 3).

The child is now 15 mo. of age and has developed normally. Height is 78 cm.; weight, 10.0 kg.

A recent gastrointestinal roentgenogram showed a normally outlined gastrointestinal tract. He has successfully withstood 2 moderate upper respiratory infections and seems to be a normal child.

Summary

A case is presented which demonstrates many of the problems encountered in treating this rare surgical emergency. The credit for a successful outcome must go mainly to the pediatricians whose close supervision and prompt therapeutic efforts were rewarded by a healthy normal infant. In the presence of a seriously damaged bowel and general peritonitis, it is difficult to imagine recovery without the streptomycin and penicillin administered. Infants are notorious for their inability to withstand any surgical procedure that allows even minor peritoneal contamination such as that occurring in bowel resection or ileostomy. According to the literature available to the authors, this is the third infant that has recovered when the omphalocele was founded ruptured at birth. All these recoveries occurred during the past few years and with the aid of large doses of antibiotics. This case also demonstrates the often life-saving value of the polyethylene venous cannula which will stay patent for days and allow continuous adequate doses of fluids, both electrolytes and blood. Demonstrated, also, is the lesson all surgeons should know—to give every case all possible aid even in the face of a seemingly hopeless pathologic state.

Conclusions

The subject of omphalocele has been briefly reviewed. Recent reports in the literature would indicate that omphalocele should no longer be associated with its previously high mortality rate.

An infant born with intrauterine rupture of the sac with strangulation of the bowel and advanced general peritonitis, with recovery, has been presented.

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Spanish Abstract

Onfalocele

Se reporta un caso de hernia umbilical congenita o "onfalocele" que sobrevivió, a pesar de la ruptura uterina del saco, estrangulación intestinal y peritonitis generalizada avanzada. Se estima que el uso liberal de antibioticos y el uso de una canula de "polyethylene" para la terapeutica intravenosa, fueron los factores decisivos en el éxito obtenido en este paciente. Los autores hacen una revisión de los conocimientos reciéntes en el tratamiento del onfalocele.

Kapiolani Street at Thomas Square

CHYLOUS ASCITES IN INFANCY

With Report of a Case with Vitamin A Absorption Studies

By DONALD GRIBETZ, M.D., AND ABRAM KANOF, M.D.
Brooklyn

EFFUSION of chyle into the peritoneal cavity occurs in childhood with extreme rarity. A careful search of the world literature has revealed only 25 cases manifesting this condition (table 1). Of these only 10, including the present case, occurred during the neonatal period. Chyloperitoneum, in association with similar effusion into the pleural or pericardial sacs, is somewhat less infrequent.[1-6] The literature also includes reports of many patients with a chyle-like (chyliform) ascites, i.e., milky effusions due to the degeneration of neoplastic cells or inflammatory conditions, but these are not included in this discussion since the resemblance of these disturbances to the chylous ascites is only superficial. The clinical differences and the contrast between the fluids chemically in the two conditions have been adequately described elsewhere.[3, 7, 8]

This report describes a case originating in the neonatal period and summarizes the pertinent literature. The results of a number of studies relating to the absorption of vitamin A in this case are also given.

CASE REPORTS

J.R., a 6 wk. old white male, was admitted with the chief complaint of constipation and abdominal distention since 3 wk. of age. The baby was a full term infant delivered by forceps because of "faulty position." Birth wt. was 4.0 kg. There was some difficulty with resuscitation, and oxygen was administered for the 1st 24 hr. He was discharged on the sixth day and circumcised on the eighth. For the 1st 10 days the infant did well. He was given a formula of similac®,* took it well, and had 3 to 4 normal stools daily.

At 3 wk. of age, he became somewhat constipated and passed a great deal of flatus, but continued to take his formula well. His abdomen, however, became progressively more distended. It was noted at this time that the baby's scrotum also was enlarging. There was neither fever nor vomiting during the entire episode. Supplementary vitamins had not been given. The infant was seen by 2 physicians during the week prior to admission, and a diagnosis of congenital megacolon (Hirschsprung's disease) was made. He was given mecholyl for 4 days with no improvement of his condition. Family history was noncontributory.

Physical examination on admission revealed a well developed and well nourished infant in no acute distress. The abdomen was symmetrically enlarged and somewhat tympanitic. There were small umbilical and ventral hernias. Shifting dullness and a fluid wave were elicited. No organs or masses were palpated. A diagnosis of ascites was made. The right side of the scrotum was swollen to the size of a chicken egg. It did not feel like a hernia but nevertheless did not transilluminate. The testicle was not palpable.

Laboratory data: Hgb. 9.6 gm./100 cc. (Sahli); RBC 3.5 million/cmm.; WBC 8.0 thousand/cmm. with 45 polymorphonuclear neutrophils, 54 lymphocytes and 1 eosinophil/100 cells. Several urine examinations were negative. Mantoux test was negative. Nose and throat cultures revealed no unusual organisms. Serum calcium was 11.6 mg./100 cc.; phosphorus 6.2 mg./100 cc. and phosphatase 12.3 Bodansky units. Blood cholesterol was 261 mg./100 cc. with a free cholesterol of 59 mg./100 cc.

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* M & R Dietetic Laboratories, Inc., Columbus, Ohio.

(22%); total lipids were 540 mg./100 cc. The prothrombin time was equal to that of the control.

Roentgenograms: A flat film of the abdomen confirmed the presence of ascites, and distention of the small and large bowel. A barium enema revealed a normal colon. RGs of the chest, skull and long bones were also normal.

Course in hospital: On admission, it was thought that the child probably had a testicular tumor with abdominal metastases and secondary ascites. Since several observers were of the opinion that there was fluid in the scrotum, a cautious scrotal tap was done and 24 cc. were aspirated. It was surprising to observe that the fluid looked like milk. Two attempts were made to drain the abdominal fluid via the scrotum but these proved unsuccessful. A paracentesis was therefore performed and 350 cc. of a similar milky fluid were removed. No masses nor abnormality of the organs were palpable after the decompression.

Description and analysis of aspirated fluid:

Appearance: yellowish-white milky fluid, pH alkaline to litmus.

Microscopic examination: there were innumerable small refractile bodies with Brownian movements among which were several larger globules about the size of leucocytes. When stained with Sudan IV, the smaller bodies coalesced and took the red stain. A Papanicolaou preparation showed round cells and leucocytes in an eosinophilic matrix with no neoplastic cells.

Chemical examination: Total lipids, 3,370 mg./100 cc.; cholesterol, 120 mg./100 cc.; vitamin A, 56 gamma %; carotene, 190 gamma %.

Culture: Sterile.

Following the paracentesis, a glucose tolerance test was done and a normal result was obtained. Vitamin A tolerance tests were performed with both aqueous and oily preparations (see chart 1) immediately after the diagnosis was established, and the test, using the oily preparation, was repeated 3 mo. later.

The first test, performed with percomorph oil, showed no absorption of vitamin A. However, when the test was repeated after administering vifort®, there was a satisfactory absorption as shown by a rise in blood level of vitamin A. Three months later, when the test was repeated with percomorph oil, there was excellent absorption as shown by a considerable rise in the blood level following the test dose.

The single paracentesis apparently resulted in a cure of the condition. The baby remained in an excellent condition and was discharged on the 17th hospital day.

Follow-up: Two months after discharge the child appeared perfectly normal. Total protein in the serum at this time was 5.0 gm./100 cc.; total lipids 440 mg./100 cc. and total cholesterol 154 mg./100 cc. Results of the vitamin A absorption test are shown in the chart. RGs of chest and abdomen and a G.I. series were normal. The patient has been observed by one of the authors since discharge and at 18 mo. seemed perfectly normal.

Discussion

Etiology and Pathogenesis: Chart 1 presents the data concerning the 25 previously reported cases. The following table summarizes the etiologic factors in these cases:

A. No etiology discovered	15 cases
1. Recovered without operation so that no search for cause was made	11
2. Operated upon but no cause found	2
3. Died and autopsied but no cause found	2
B. Etiology discovered	
1. At operation	7
a. Enlarged mesenteric glands producing pressure on the chyle duct	4
b. Adhesions from previous operations	2
c. Tumor in region of the vertebral column	1
2. At post mortem	3
a. Marked stenosis of the thoracic duct	2
b. Enlarged tuberculous mesenteric glands	1

Although one of the earliest instances of chylous ascites was reported by Virchow[9] in a newborn calf with thrombosis of the subclavian vein at the point where the duct empties

TABLE 1

ESSENTIAL FINDINGS IN 25 CASES OF CHYLOUS ASCITES FOUND IN LITERATURE

Author	Age at Onset	Sex	Etiology	Clinical Course	Treatment	Outcome
1. Winiwater,[24] 1877	At birth	F	"Congenital occlusion of thoracic duct, cyst formation and rupture and continuous effusion of chyle through this rupture."	Gradually increasing abdominal distension and constipation since birth. Vomiting.	Repeated taps	Died
2. Kerr,[25] 1909	At birth	M	None found	Gradually increasing abdominal distension. Scrotum enlarged.	Repeated taps	Rec.
3. Cowie,[26] 1909	At birth	M	None found	Abdomen markedly enlarged at birth, and continued to increase. Vomiting, scrotum enlarged.	Repeated taps	Rec.
4. Kamienski,[27] 1895	At birth	M	None found	Abdomen distended from birth. Later vomiting and diarrhea. Transient navel discharge at birth. Scrotum enlarged.	Repeated taps	Rec.
5. Wegner,[13] 1934	At birth	M	Not determined at exploratory operation	Huge abdomen and scrotum from birth, neglected to 5 mo. of age but no worse for it.	Exploratory at 5 mo. Repeated taps. Venous peritoneal anas. at 8 m.o.	Rec.
6. Finkelstein,[28] 1924	At birth	F	At autopsy, striking stenosis of thoracic duct	Progressive enlargement of the abdomen from birth, in a typical mongol.	Repeated taps	Died
7. Author's case, 1950	At birth	M	None found	Gradually increasing abdominal distension, constipation and enlarged scrotum.	Repeated taps	Rec.
8. Smidt Van Gelden,[29] 1920	At birth	?	None found	Large abdomen at birth, becoming larger. Repeatedly filled up after tap until suddenly recovered at 11 mo. of age.	Repeated taps	Rec.
9. Wyatt and Gross,[10] 1941	6 wk.	M	Adhesions from operation for intestinal obstruction at age of 6 days	Abdomen distended. X-ray findings of radiopaque liver and translucent surrounding fluid.	Operation and relief of adhesions	Rec.
10. Schall,[30] 1922	3 mo.	F	None found at autopsy	Vomiting and diarrhea began at 3 mo. after weaning. Abdomen enlarged, diagnosed Hirschsprung's disease. Died after laparotomy from cardiac failure.	Laparotomy and drainage	Died
11. Bruchsaler,[31] 1929	4 mo.	M	At autopsy, edema in the region of the thoracic duct. Author uncertain about its importance.	Sudden onset, abdominal distension and vomiting.	Talma operation: omentum inserted into pocket in left abdominal wall.	Died
12. Bossard,[32] 1937	7 mo.	F	None found. Child killed in accident 3 mo. after recovery. No cause found for ascites, at autopsy.	Increasing size of abdomen, dyspnoea.	Repeated taps.	Rec.

Author	Age at Onset	Sex	Etiology	Clinical Course	Treatment	Outcome
13. Wilhelms,[33] 1874	8 mo.	F	Tumor mass at vertebral column	Gradually increasing abdominal distention beginning at 2 mo. after recovery from pertussis.	Exploratory operation. Repeated taps.	Rec.
14. Willi,[34] 1936	11 mo.	F	None found	Increasing abdominal size soon after birth.	Repeated taps	Presumably rec.
15. Nieuwondt and Rosenzweig,[35] 1892	Before 15 mo.	F	None found	Emaciation, diarrhea, vomiting, and abdominal distention.	Repeated taps (11)	Rec.
16. Morton,[36] 1691	Before 2 yr.	M	Pressure on duct from probable tuberculous glands. Autopsy.	Fever, cough, emaciation. Tap during life revealed pure "lactescent chyle as sweet as found in the chyle duct itself."	Tap. Venesection, liniments etc. (Reported in 1691)	Died
17. Newcomb,[37] 1889	2 yr.	M	None found	5 day history abdominal enlargement and pain with later onset of dyspnoea.	Repeated taps	Rec.
18. Davis,[26] 1939	2 yr.	M	Mesenteric glands	Repeated attacks of abdominal pain relieved by standing patient on head. At operation at age of 4 yr., found chyle cyst wedged into pelvis.	Cyst excised	Rec.
19. Letulle,[39,40] 1885	2½ yr.	M	Possible congenital heart disease resulting in hepatic cirrhosis and peritoneal adhesions causing obstruction of duct.	Pallor, emaciation and enlargement of abdomen. Scrotum distended; liver very large. No cardiac murmurs.	Repeated taps	Rec.
20. Huber and Silver,[41] 1914	8 yr.	M	Possibly secondary to pressure of large glands at root of mesentery.	Measles at 7 mo. with edema of extremities. At 7½ yr. gradual increase in size of abdomen, edema of scrotum and thighs. Enlarged lacteals and mesenteric glands at operation.	Operation: anastomosis of iliac vessels to peritoneum.	Rec.
21. Smith, quoted by Busey,[42]	9 yr.	M	None found	Good general health	Repeated taps. 28 pints removed in 21 days	Rec.
22. Button,[14] 1946	10 yr.	F	Possible blow to abdomen. Old history of tuberculosis peritonitis but no evidence at operation.	Transitory swelling of abdomen at 5 yr. of age. Collided with bench at 9 yr. of age. Abdominal swelling 2 wk. later—Paracentesis revealed chyle. Intervals between taps decreased; patient lost ground. Operation.	Repeated taps. Anastomosis of int. saphenous vein to peritoneum	Rec.
23. Davis,[26] 1939	12 yr.	M	Secondary to enlarged mesenteric glands	Acute abdominal pain 10 mo. after operation for ruptured appendicitis. Found marked enlargement of glands at base of mesentery and marked distention of lacteals.	Exploratory and drainage	Rec.
24. Pratt and McCready,[43] 1949	15 yr.	F	Adhesions following operation, seem to constrict base of mesentery.	6 wk. after operation (subtotal colectomy and end-to-end ileorectosigmoidostomy) began to suffer acute abdominal pain and vomiting.	Operation and section of adhesive band	Rec.
25. Davis,[26] 1939	15 yr.	F	Secondary to enlarged glands at base of mesentery.	Sudden onset of abdominal pain and vomiting. Chyle cyst found at operation.	Marsupialization of cyst. Twice	Rec.

into the venous circulation, and although such cause has been found clinically in adults and has been produced experimentally in dogs, no such case has been found in childhood. Neither have the authors found a case due to a wound, although this cause too has been reported in adults.

It has been postulated that in the "spontaneous" cases with recovery, a congenital defect or a hypoplastic configuration of the large lymphatic vessels causes a blockage which produces dilatation of the smaller lymphatics due to back pressure and that this allows seepage of lymph across the vessel walls.[4] A congenital weakness of the lymph channels allowing escape of the chyle is another theory. One can only speculate on these possibilities and on the factors leading to their spontaneous alleviation.

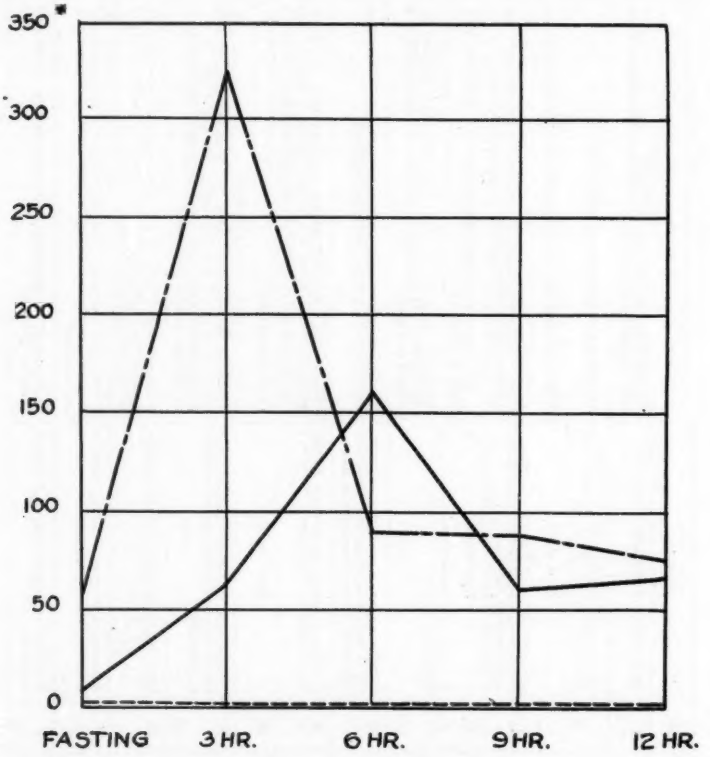

CHART 1. Vitamin A Tolerance

---------- Test performed with 0.1 cc. oleum percomorphum† /lb. body weight during first admission.

———— Test performed with 1.2 cc. vifort®‡ /lb. (12,000 u./lb.) during first admission.

— — Test performed with 0.1 cc. oleum percomorphum/lb. 3 mo. later.

* Vitamin A is expressed as μg./100 cc. One microgram is equivalent to 3.57 U.S.P. units.

† Oleum percomorphum (Mead Johnson) is composed of the liver oils of percomorph fishes reinforced with viosterol and other fish liver oils. It contains 60,000 u. vitamin A and 8,500 u. vitamin D/gm.

‡ Vifort® (Endo Products) is a water dispersible polyvitamin preparation. Each 0.6 cc. contains 5,000 u. vitamin A and 1,200 u. vitamin D in addition to vitamins of the B complex group.

Roentgenography: Attempts were made in reviewing the RGs of this case to confirm the findings of Wyatt and Gross.[10] In films of their case of chylous ascites in an infant, they were able to demonstrate a marked difference in the density of the liver as compared to that of the surrounding ascitic fluid. The latter was more radiolucent. Since it is known that fatty fluids are radiolucent and since this feature is contrary to that in other ascitic fluids, they predicted from their RGs that the ascites was chylous. The present investigators were unable to confirm their findings. Ferrara and Walker[11] were also unable to demonstrate this radiographic sign in their case.

Chylocele: Five of the 25 patients, including the one reported here, also had chylous fluid in the scrotum. In all five the disease started in the neonatal period. The partially open condition of the tunica vaginalis during that period explains this occurrence. In the other five patients observed in the neonatal period, only one was a male child and no mention is made of the condition of his scrotum. Among the 14 patients observed in infancy or childhood (Cases 11, 9 and 20), two were reported to have edema of the scrotum. Busey[12] gives reports of cases of lymphocele in which there was dilatation of the lymphatic vessels in the scrotum and rupture with free lymph in the tunica vaginalis, independent of the state of the peritoneum. These are naturally different from the cases summarized by the present authors where the fluid in the scrotum comes by direct extension from the peritoneal cavity.

Treatment and Prognosis

The following is a tabulation of the treatment and outcome of the 22 reported cases:

A. Treated with paracentesis alone	14 cases
1. Recovered	11
2. Died	3
a. Mongolism	1
b. Poor supportive treatment (Cases 1 and 16)	2
B. Treated with surgical procedures	
1. Relief of adhesions	2
Recovered	2
2. Procedures for establishment of auxiliary pathways for drainage of chyle	4
Died (Talma operation—omentum inserted into abdominal wall)	1
Recovered (anastomosis of iliac vessels and peritoneum)	3
3. Exploratory operation	3
Recovered	1
Died	2
4. Excision of a lymphatic cyst	2
Recovered	2

Treatment in the case reported here was conservative and expectant. The complete recovery of the patient, and that of 11 of the 14 previously reported cases treated with paracentesis alone, support the point of view that in any such case conservative treatment consisting of paracentesis and supportive measures should be attempted before resort to surgical measures. In passing it should be mentioned that the present patient was unique in that only one paracentesis was necessary; most of the reported cases required many more before recovery was complete. It is also emphasized that the difficulty in finding the defect even at postmortem examination, plus the small size and delicacy of lymphatic structures in this age group, make it unlikely that surgical attempts to find the etiology in infants will be successful. After failure of repeated paracentesis, surgery for the purpose of removing gross tumors or cysts, relieving adhesions or bands, or for performing

a palliative anastomosis may be undertaken. Of the last named the most successful procedure seems to be that of Routte in which the great saphenous vein is divided and the distal end of the proximal segment is sutured to the parietal layer of the peritoneum. This procedure is fully discussed and described elsewhere.[13,14]

Although it was never considered in the case reported here since only one paracentesis was required, the possibility of reintroducing the aspirated chyle intravenously in cases where the losses are great should be considered. Little, Harrison and Blalock[15] carried out this procedure in their case of a 17 year old girl with a traumatic chylothorax and were impressed with the results. On the other hand, some of the patients tabulated had several taps involving withdrawal of great amounts of fluid with no replacement of chyle and with complete recovery. There is no doubt, however, that supportive therapy is essential and that replacement of protein lost in chyle is quite as important as replacement of fat.

Vitamin A Metabolism: The studies concerning vitamin A metabolism in this case yielded interesting data. The fasting level of serum vitamin A was zero. Following this 72,000 units of vitamin A were given as oleum percomorphum. Two days later the fasting level was 7 μg./100 cc. indicating that some vitamin A was absorbed even though none was found 3, 6 or 9 hours after the above dose. At this time 125,000 units of aqueous "A" was given as vifort®. Ten days thereafter the fasting level dropped to 1 μg./100 cc. These low fasting levels when compared to the normal of this age group[16] may be explained by the fact that most of the absorbed vitamin A went into the chyle. (See analysis of chyle.)

In the first test of vitamin A absorption a large dose of oleum percomorphum (6,000 units/pound) was administered orally. The fasting level was zero and there was no change in this 3, 6 and 9 hours after the vitamin A intake. The ingested vitamin did not appear in any of the subsequent blood samples. Although concomitant samples of chyle could not be obtained, it is assumed that practically all the administered vitamin in the test dose went into the chyle and none into the blood stream. This is in agreement with observations made by Drummond and his co-workers[17] who observed a patient with a fistula of the thoracic duct opening into the pleural cavity. After administration of vitamin A to their patient, nearly all of it could be recovered in the chest fluid.

To determine whether it is possible to administer vitamin A orally, the vitamin A tolerance was repeated two days later with aqueous A because it had been shown earlier (1946) in this laboratory that vitamin A in aqueous dispersion is absorbed more readily than when administered in oil.[16,18,19] An aqueous dispersion of vitamin A (vifort®*) 125,000 units was used. In this test it can be seen that a rise in the blood vitamin A was produced, although the curve was lower than normal. These findings have been duplicated by Forbes[4] and Wessel[5] who studied vitamin A metabolism in a similar manner in cases of chylothorax in infancy.

Clausen[20] cites unpublished work by McCoord et al. who produced thoracic duct fistulae in dogs. After vitamin A was fed, much of it appeared in the lymph of the thoracic duct but the vitamin A content of the blood was also increased rapidly. Clausen suggests that in the dog it may be possible that vitamin A is absorbed not only by the lymphatics but also by the blood capillaries of the small intestine.

The experimental studies of Frazer[21,22] suggest an explanation both for the present

* Endo Products Inc., Richmond Hill, New York.

authors' observations and for Clausen's hypothesis. Frazer presents evidence to indicate that there are two mechanisms for the absorption of ingested fat. A large portion passes into the lymphatic system where it circulates in the chyle and is then carried to the venous circulation. The remaining portion passes directly into the portal system and does not increase the chylo-micron content in the blood. This "partition hypothesis" is dependent directly on particle size in an aqueous dispersion. From the studies of the present investigators, it is evident that no oleum percomorphum appeared in the blood during the first vitamin A tolerance test but rather that the material was absorbed into the defective lymphatic system and appeared in the ascitic fluid. Most of the absorption of this material must have taken place by the first of the two routes proposed by Frazer. Normal amounts, however, appeared in the blood stream when the procedure was repeated three months later. On the other hand, the vifort®, which is an aqueous dispersion in which the particle size of the vitamin A containing oil is less than 0.5 μ in diameter (not visible under a microscope—barely perceptible under ultra-microscope) and which was administered at about the same time as the first test with oleum percomorphum, did appear in the blood stream. It can only be concluded that the vitamin A in the vifort® was absorbed by some other mechanism, probably that of particulate absorption directly into the blood capillaries as suggested by Frazer.

It is suggested by these observations that where defective fat absorption exists these substances should be administered in an aqueous dispersion in which the particle size is greatly reduced. Kramer and his coworkers[16] and May and Lowe[23] conducted experiments with other types of defects in fat absorption, i.e., lack of intestinal enzymes and defects in the intestine itself and came to similar conclusions: that aqueous dispersions in which the particle size was very small would overcome the difficulty.

Summary and Conclusions

A description of a case of chylous ascites with chylocele unassociated with chylous fluid in any other of the body cavities is described. The literature is reviewed and a summary of four similar cases is presented. The 25 cases in the literature are analyzed in terms of etiology, association of chylocele, roentgenographic findings, treatment and prognosis.

It is suggested that all such cases, particularly when they occur in the newborn infant, should be treated with conservative measures, i.e., paracentesis and supportive management, before resort to laparotomy.

Studies concerning the absorption of vitamin A are presented which indicate that where defects in fat absorption through lymphatic pathways exist, the use of aqueous dispersions of fat soluble vitamins ensures their absorption into the general circulation.

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SPANISH ABSTRACT

Ascitis Quilosa en la Infancia. Reporte de un Caso con Estudios en la Absorción de la vitamina A.

Los autores indican que solamente 25 casos de ascitis quilosa pura, sin efusiones concomitantes en otras cavidades del cuerpo han sido reportados. La etiologia de esta condicion puede ser debida a una compresion externa o a una estenosis del conducto linfatico, aunque la mayoria de las veces la causa se desconoce. Estudios de absorción de vitamina A en este caso demostraron un defecto en la absorción del quilo atráves de las vias linfaticas. Sin embargo, la absorción tuvo lugar cuando la vitamina. A fué administrada en suspension acuosa. En aquellos casos raros causados por una obstrucción, el tratamiento quirurgico puede estar indicado, pero la mayoria de los casos responden bien a las paracentesis y tratamiento sintomatico.

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VOLUMETRIC AND MICROSCOPIC PATTERN OF BONE MARROW IN NORMAL INFANTS AND CHILDREN

II. Cytologic Pattern

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THE volumetric pattern of bone marrow aspirated from the tibia, iliac crest and sternum of infants and children was presented in a previous report.[1] The data from 40 tibial aspirations performed on individuals from birth to 5 years of age revealed that after 2½ years of age the majority gave high fat values and low values for the myeloid-erythroid layer. The interpretation was that the marrow of the tibia tends to become relatively fatty and hypoplastic early in life. In contrast, 22 iliac aspirations from individuals 18 months to 12 years of age and 10 sternal aspirations from individuals 4 to 12 years of age gave similar volumetric data which were comparable to that reported for sternal aspirations from older individuals.

The purpose of this report is (1) to present the cytologic pattern prepared from the myeloid-erythroid layers of the preceding aspirations, (2) to ascertain if there are changes in these data in relation to growth and (3) to compare the percentage distribution of cells obtained by this volumetric and concentration technic to that reported in the same age range where direct smears were examined.

METHOD OF STUDY

The normal subjects employed for this study and the sites and technic of aspiration were described previously.[1] The equipment used in preparation of the smears for staining and microscopic study was also illustrated.

To prepare the microscopic slides, equal volumes of plasma myeloid-erythroid and packed red blood cells were withdrawn from the hematocrit tube and mixed on the paraffin-lined watch glass. A drop of the mixture was spread on a warmed glass slide with a hemocytometer cover slip held by means of an artery clamp. Five smears were made from each aspiration. They were stained with domestic Wright's stain for 15 min. and then decolorized by Schleicher's method.[2]

Differential counts under oil immersion of approximately 1500 magnification were performed on 2 slides counting 500 cells; these were averaged. "Smudge" or "ruptured" cells were not included in the counts.*

The various nucleated cells were classified as indicated in the headings in table 1. The cells of the erythrocytic series were subdivided into the stages of maturation employed by Sundberg.[3] The granulocytic and lymphocytic series of cells were classified as outlined in the report of the Committee for the Clarification of the Nomenclature of Cells and Diseases of Blood-forming Organs.[4] The myelocytes were divided into early and late forms. The cells of the granulocytic series with a round or oval nucleus, having a nuclear structure slightly more coarse than the progranulocyte and a cytoplasm which still showed considerable basophilia surrounding a small focal accumulation of

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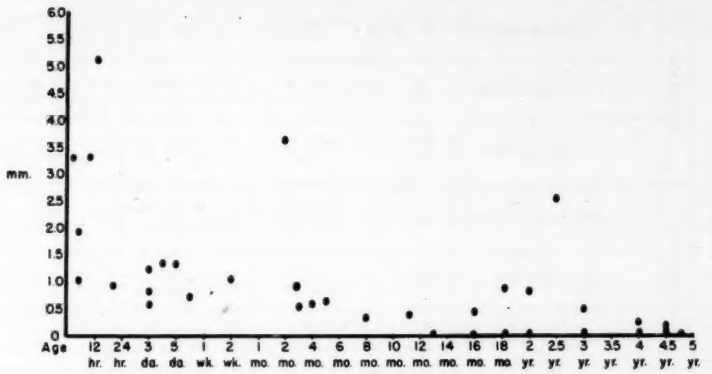
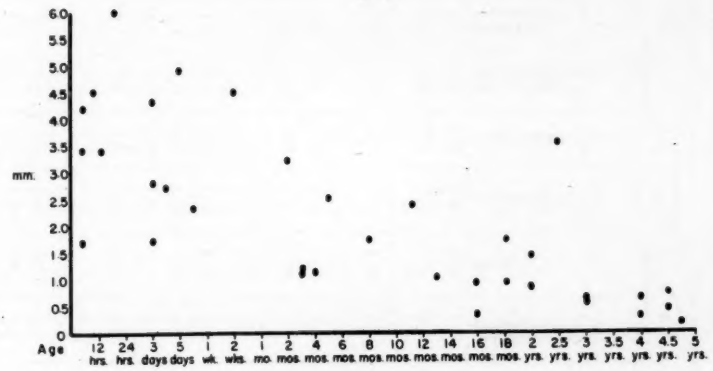
* Some of the specimens were unsatisfactory for differential counting because the great majority of cells were distorted. This was found only in those prepared from newborn infants and was unavoidable because the aspirations had to be performed at another hospital. The delay in processing the heparinized material was as much as 1½ hr.



A



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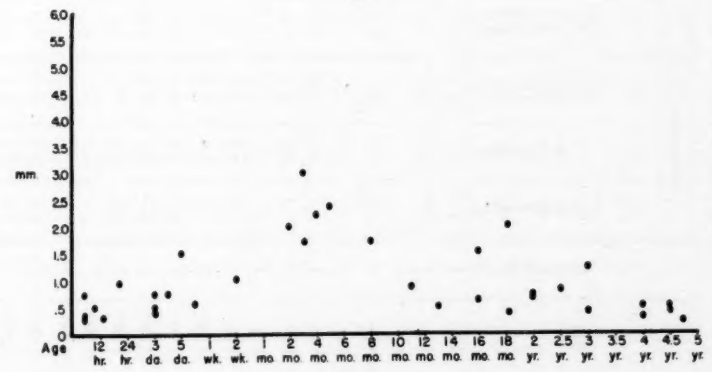

C

CHARTS 1A, B and C. Influence of Age on Total Normoblasts, Granulocytes and Lymphocytes. A. Normoblastic ME. B. Granulocytic ME. C. Lymphocytic ME.

TABLE 1

PERCENTAGE DISTRIBUTION OF NUCLEATED CELLS FOUND ON 72 MARROW ASPIRATIONS FROM 50 NORMAL INFANTS

Subject No.	Age	Site of Aspiration	Erythrocytic			Granulocytic									Lymphocytic			Other Cells		
							Neutrophiles				Eosinophiles									
			Pronormoblasts, %	Basophilic, %	Polychromatic and Orthochromatic, %	"Myeloblasts" and Progranulocytes, %	Early Myelocytes, %	Late Myelocytes and Metamyelocytes, %	Band, %	Segmented, %	Early Myelocytes, %	Myelocytes and Metamyelocytes, %	Band and Segmented, %	Basophiles, %	"Lymphoblasts," %	Prolymphocytes, %	Late Lymphocytes, %	Monocytes, %	Plasma Cells, %	Megakaryocytes[1]
1	5 hr.	T	1.2	1.8	41.2	0.1	0.5	1.3	13.4	26.0	0.0	0.0	1.8	0.2	0.0	0.1	6.8	5.6	0.0	39
2	5 hr.	T	2.4	1.5	33.9	0.0	1.5	4.4	17.7	21.9	0.0	0.2	1.6	0.0	0.5	0.2	7.3	6.9	0.0	31
3*	5 hr.	T																		50
4	5 hr.	T	0.4	0.9	20.4	0.7	0.6	3.1	20.6	39.0	0.1	0.7	2.2	0.0	0.1	0.1	6.5	4.6	0.0	30
5*	7 hr.	T																		30
6	9 hr.	T	1.5	2.1	33.8	0.2	1.1	3.7	22.9	20.0	0.0	0.9	1.1	0.2	0.1	0.2	4.9	7.3	0.0	68
7	13 hr.	T	2.5	2.6	51.0	0.6	1.3	5.4	20.3	9.6	0.0	0.2	0.8	0.0	0.0	0.1	3.6	2.0	0.0	36
8†	15 hr.	T																		
9	18 hr.	T	0.4	0.4	9.5	0.1	2.0	7.3	39.9	15.5	0.1	0.5	1.3	0.1	0.0	0.0	10.8	12.1	0.0	§
10	3 days	T	1.0	1.0	11.4	1.9	1.9	11.0	31.8	22.8	0.1	0.5	1.4	0.0	0.0	0.2	9.3	5.7	0.0	§
11	3 days	T	0.5	0.5	23.2	0.7	1.0	5.6	22.0	25.7	0.0	0.6	1.3	0.0	0.5	0.8	14.6	3.0	0.0	72
12	3 days	T	0.4	0.2	19.6	1.3	1.9	7.0	17.4	30.2	0.1	0.5	3.0	0.2	0.2	0.7	12.8	4.5	0.0	135
13	4 days	T	0.7	0.8	24.5	1.1	2.2	12.6	27.6	8.7	0.0	0.2	1.4	0.0	0.1	0.6	15.0	4.5	0.0	§
14‡	4½ days	T																		61
15*	4½ days	T																		104
16	5 days	T	0.8	0.5	15.3	1.5	2.5	16.3	21.0	19.1	0.0	1.5	1.5	0.0	0.1	0.6	18.1	3.2	0.0	§
17	6 days	T	1.1	0.3	17.1	0.4	1.0	6.7	17.8	25.8	0.2	1.0	4.1	0.2	0.1	0.9	12.9	10.2	0.2	97
18	2 wk.	T	1.6	1.2	11.5	2.5	4.5	11.5	32.4	7.6	0.1	2.5	3.4	0.0	0.0	0.3	3.9	6.8	0.0	227
19	2 mo.	T	0.8	1.8	36.9	0.5	1.3	6.6	18.7	6.7	0.0	0.8	1.3	0.0	0.0	0.3	21.8	2.3	0.2	257

20	3 mo.	T	0.3	1.9	22.0	0.2	1.2	2.6	8.9	11.5	0.0	1.0	2.7	0.1	0.1	0.5	41.7	5.3	0.0	104
21	3 mo.	T	0.2	0.2	12.7	0.8	1.9	4.4	7.7	3.7	0.0	2.4	1.5	0.0	0.3	1.2	58.3	4.7	0.0	§
22	4 mo.	T	1.6	0.4	12.2	0.6	0.4	4.2	16.6	3.5	0.1	0.5	2.2	0.1	0.1	1.4	53.7	2.4	0.0	§
23	5 mo.	T	0.2	0.1	10.3	0.7	2.6	11.0	15.7	10.6	0.0	1.4	1.8	0.2	0.2	1.3	35.7	8.0	0.2	155
24	8 mo.	T	0.7	0.6	5.9	1.0	2.1	7.8	17.4	11.0	0.2	1.2	1.4	0.0	0.0	0.4	43.0	7.1	0.2	473
25	11 mo.	T	0.6	0.7	8.8	0.5	1.4	1.8	5.9	48.5	0.1	0.4	0.4	0.0	0.0	0.0	23.9	6.8	0.2	172
26	13 mo.	T	0.1	0.2	2.3	0.1	0.8	4.3	10.1	50.4	0.0	0.2	0.2	0.0	0.0	0.0	31.3	0.0	0.0	§
27	16 mo.	T	0.0	0.0	0.9	0.1	0.2	0.6	1.4	20.6	0.0	0.2	4.5	0.4	0.0	0.0	56.3	14.8	0.0	22
28	16 mo.	T	0.2	0.4	12.8	0.1	0.5	4.5	11.4	12.5	0.0	1.1	1.4	0.1	0.1	0.5	49.0	5.1	0.3	86
29	19 mo.	T	0.2	0.0	2.2	0.1	1.6	2.7	19.8	34.1	0.1	0.1	3.1	0.8	0.0	0.2	25.3	9.6	0.1	10
		I	0.3	0.4	12.6	0.2	1.8	4.4	22.9	16.8	0.0	1.0	2.8	0.5	0.0	0.6	31.3	4.3	0.1	109
30	19 mo.	T	2.2	2.2	13.0	0.7	0.8	5.8	9.9	9.7	0.2	4.1	3.3	0.3	0.0	0.0	41.8	5.5	0.5	212
		I	1.1	2.2	17.3	1.1	1.7	6.3	12.2	14.0	0.2	3.7	3.8	0.2	0.0	0.1	32.0	4.1	0.0	209
31	2 yr.	T	0.0	0.0	0.0	0.0	0.0	0.0	4.2	66.9	0.0	0.0	0.0	0.1	0.0	0.0	23.0	5.8	0.0	3
		I	1.4	1.5	29.0	0.6	1.1	3.7	12.5	9.6	0.2	1.7	2.7	0.2	0.0	0.1	28.3	7.1	0.3	41
32	2 yr.	T	1.0	0.3	30.3	0.4	1.8	3.4	15.3	10.1	0.0	1.6	0.8	0.2	0.8	2.1	26.5	5.1	0.3	120
		I	0.4	0.4	26.7	0.8	2.5	3.6	15.4	23.1	0.1	1.9	2.6	0.4	1.0	3.0	25.3	2.6	0.2	160
33	2 yr.	T	0.3	0.5	8.9	0.8	3.5	8.5	31.2	17.7	0.1	1.9	1.1	0.2	0.0	0.2	12.4	12.3	0.4	317
		I	0.8	2.0	32.3	0.6	1.9	2.8	19.4	22.4	0.0	0.9	1.6	0.3	0.0	0.2	11.0	3.6	0.2	122
34	3 yr.	T	0.9	0.9	15.5	0.7	1.2	2.5	8.5	7.2	0.1	2.0	2.1	0.1	0.2	1.0	46.4	10.6	0.1	145
		I	1.5	1.3	22.8	0.6	2.5	4.9	12.5	7.8	0.1	3.4	0.8	0.2	0.2	0.6	34.4	6.2	0.2	122
35	3 yr.	T	0.0	0.0	0.4	0.1	0.2	0.8	4.4	43.3	0.0	0.1	1.5	0.0	0.0	0.2	41.6	5.9	1.5	7
		I	1.3	1.4	17.7	1.1	3.9	7.8	22.9	17.2	0.1	2.0	2.1	0.0	0.0	0.2	16.8	5.0	0.5	172
36	4 yr.	T	0.0	0.3	18.5	0.1	0.4	4.3	6.1	12.0	0.0	0.8	1.7	0.1	0.0	0.4	44.0	10.8	0.5	12
		I	0.9	0.8	26.2	0.7	1.8	4.2	19.0	10.3	0.1	2.1	2.1	0.1	0.1	0.3	21.4	9.4	0.5	95
37	4 yr.	T	0.0	0.0	0.3	0.3	0.1	0.3	2.4	46.2	0.0	0.2	7.3	0.8	0.0	0.1	31.8	10.2	0.0	13
		I	0.5	1.4	17.9	1.2	2.3	7.5	18.7	13.2	0.2	2.2	4.7	0.1	0.1	0.5	21.0	8.5	0.0	105
38	4 yr.	T	0.3	0.3	17.4	0.1	2.2	6.1	12.3	14.3	0.1	2.0	1.3	0.1	0.1	0.6	36.3	6.3	0.2	161
		I	0.3	00.7	28.3	0.9	1.5	6.4	10.3	14.5	0.2	2.8	1.4	0.1	0.1	1.0	25.4	5.6	0.5	219
39	4 yr.	T	0.2	0.4	4.0	0.1	0.4	2.5	5.5	36.9	0.1	0.8	0.9	0.0	0.0	0.1	32.8	15.2	0.1	14
		I	2.6	1.4	18.1	1.0	1.8	6.0	19.6	9.7	0.1	3.4	3.0	0.3	0.1	0.2	26.0	6.7	0.0	101
40	4 yr.	T	0.1	0.0	1.1	0.2	0.4	1.7	3.9	22.0	0.0	0.1	4.7	0.7	0.0	0.0	43.3	21.4	0.4	14
		I	0.8	0.8	33.6	0.6	2.1	7.3	14.6	8.2	0.1	2.0	3.3	0.3	0.0	0.1	21.6	4.5	0.1	118

TABLE 1—(*continued*)

Subject No.	Age	Site of Aspiration	Erythrocytic			Granulocytic									Lymphocytic			Other Cells		
							Neutrophiles				Eosinophiles									
			Pronormoblasts, %	Basophilic, %	Polychromatic and Orthochromatic, %	"Myeloblasts" and Progranulocytes, %	Early Myelocytes, %	Late Myelocytes and Metamyelocytes, %	Band, %	Segmented, %	Early Myelocytes, %	Myelocytes and Metamyelocytes, %	Band and Segmented, %	Basophiles, %	"Lymphoblasts," %	Prolymphocytes, %	Late Lymphocytes, %	Monocytes, %	Plasma Cells, %	Megakaryocytes[1]
41	5 yr.	S	2.1	2.0	21.9	0.3	3.6	6.4	15.1	13.3	0.0	2.7	2.7	0.3	0.0	0.5	22.3	6.7	0.1	227
		I	1.4	1.8	24.8	0.7	3.9	5.9	17.5	15.1	0.2	2.5	3.9	0.2	0.1	0.2	15.9	5.8	0.1	151
42	6 yr.	S	0.2	0.6	7.3	1.0	1.2	5.2	25.6	31.1	0.1	0.9	1.7	0.2	0.1	1.0	17.4	5.2	1.2	101
		I	0.7	0.8	16.3	0.9	2.6	7.3	22.8	19.2	0.0	1.2	0.8	0.2	0.0	0.4	21.1	4.9	0.8	171
43	6 yr.	S	0.8	1.6	22.2	0.6	2.1	6.3	12.5	23.0	0.0	1.2	5.3	0.2	0.0	0.1	18.8	5.1	0.2	45
		I	2.0	2.5	30.7	0.6	1.6	5.1	11.5	9.0	0.3	2.8	3.2	0.2	0.2	0.4	26.9	2.6	0.4	152
44	7 yr.	S	0.8	0.8	31.2	0.3	1.5	7.2	26.0	9.0	0.0	2.5	3.5	0.0	0.0	0.2	†15.8	0.4	0.8	177
		I	1.2	1.7	22.7	0.4	2.3	8.9	23.4	15.9	0.0	2.8	2.0	0.3	0.0	0.0	18.0	0.4	0.0	89
45	7 yr.	S	2.0	2.3	32.1	0.2	1.6	6.5	17.7	8.3	0.2	2.8	1.7	0.1	0.1	0.3	19.6	4.4	0.1	239
		I	1.6	1.5	33.6	0.5	1.1	9.9	19.1	6.1	0.0	2.5	2.4	0.0	0.1	0.1	16.5	4.7	0.3	266
46	8 yr.	S	1.2	1.4	29.9	1.6	1.6	7.8	21.4	22.8	0.0	2.0	2.7	0.2	0.2	0.3	15.3	1.5	0.1	94
		I	1.1	1.6	16.4	0.4	0.8	7.6	22.9	16.9	0.2	1.4	1.0	0.3	0.1	0.3	20.6	7.5	0.9	172
47	10 yr.	S	0.0	0.1	4.8	0.1	0.5	2.6	12.5	45.4	0.0	0.1	2.3	0.2	0.0	0.0	19.7	10.2	1.5	55
		I	0.1	0.1	9.1	0.3	1.3	3.3	13.6	50.0	0.0	0.1	2.8	0.2	0.0	0.0	15.3	2.9	0.9	47
48	11 yr.	S	1.4	4.0	27.4	0.8	2.1	7.1	14.9	15.5	0.0	1.9	1.6	0.0	0.1	0.3	16.6	5.6	0.7	279
		I	1.3	2.7	28.3	1.0	1.8	6.2	13.0	14.8	0.0	1.0	1.7	0.4	0.2	0.7	19.2	7.0	0.7	211
49	11 yr.	S	0.2	0.8	13.8	0.5	0.7	6.5	31.2	15.8	0.1	1.6	0.9	0.1	0.1	0.4	17.7	8.7	0.9	189
		I	0.4	0.7	23.2	0.9	2.3	7.1	19.4	20.9	0.2	3.2	1.6	0.2	0.0	0.2	13.2	6.0	0.5	63
50	11 yr.	S	0.4	1.1	14.5	0.2	2.0	5.8	18.8	19.7	0.1	2.5	3.5	0.2	0.0	1.7	22.3	6.4	0.8	228
		I	1.4	1.3	23.3	0.5	2.5	3.8	12.9	18.5	0.1	1.9	3.9	0.0	0.0	1.8	25.0	2.7	0.4	271

[1] All megakaryocytes counted on terminal 20 mm. of smear.
* Smear unsatisfactory for counting.
† No marrow obtained.
‡ ME read improperly.
§ Clotted. Specimen not suitable for megakaryocyte count.

specific granules adjacent to the nucleus, were classified as early myelocytes. Late myelocytes included the rest of the myelocytes; these were grouped with the metamyelocytes.

It is well recognized that the blast cells are morphologically quite similar; hence, the headings of these columns in table 1 are placed in quotation marks. In general, the blast cells were placed in their respective categories on the basis of closely adjacent pro- and more mature stages.

Megakaryocytes were enumerated, as described by Schleicher,[5] on the terminal 20 mm. of the smear, using a 50× magnification. One of the remaining 3 stained smears was selected for the megakaryocyte counts. Twenty millimeters from the feathered edge of the smear, a base line was drawn across the slide transverse to the direction of the smear. Several parallel lines were then drawn from the base line through the feathered edge. Then, under low power, using the parallel lines as guides, all the megakarocytes enclosed between the several parallel lines were counted.

Results

Table 1 lists the cases in the order that they appeared in the previous report.[1] It gives the percentage distribution of all the nucleated elements noted.

Tibia: The percentage of normoblasts tends to decrease from an average level of approximately 40% in the five cases from 5 to 13 hours old to an average of approximately 8% in the 5 cases in the 4 year old range. However, averages are quite misleading because several of the cases showed values of less than 1% normoblasts in the group from 2 to 4 years of age. On the other hand, even in the 4 year old group some relatively high values were obtained (18%). After two years the general tendency is for the percentage of normoblasts from the tibia to diminish toward zero (see table 1).

Chart 1A illustrates a more absolute value for normoblasts obtained from the tibia. This value, the "Normoblastic ME," was obtained by multiplying the millimeters of the myeloid-erythroid layer times the per cent/hundred normoblasts. The resultant figure expressed the millimeters of the myeloid-erythroid layer that were considered to be composed of normoblasts.

The percentage of granulocytes in general does not show the rapid decrease in value after eight months that was noted in most cases for the normoblasts. However, because of the general tendency for the myeloid-erythroid layer to decrease, the "Granulocytic ME" shows a marked decrease with increasing age but does not reach the lower values noted for the "Normoblastic ME."

The percentage of lymphocytes shows a distinct increase with age, starting at values of less than 10% in the first week of life and reaching levels of over 40% in the four year range (see table 1). Chart 1C, however, illustrates that this is more relative than absolute inasmuch as the "Lymphocytic ME" appears to remain relatively constant in contrast to the "Normoblastic" and "Granulocytic ME."

Iliac Crest and Sternum: In the group where the iliac crest and sternum were studied, age does not have the apparent influence on the percentage distribution of cell types that it does on the values from the tibia. This parallels the apparent lack of influence of age on the volumetric data reported previously for this group. Inspection of scatter graphs plotted for both sites in a manner similar to charts 1A through C likewise showed no influence of age on the "Normoblastic," "Granulocytic" or "Lymphocytic ME." The average percentage value for the major groups of cells and their range of values showed little variation between the two sites. Table 2 summarizes these data.*

* From the inspection of table 1, it can be seen that the lowest values for the per cent normoblasts from the ilium and sternum and the highest values for the per cent granulocytes from these 2 sites recorded in table 2 were all obtained from Case 47. The ranges for these values is considerably less if Case 47 is eliminated.

TABLE 2

AVERAGE AND RANGE OF PERCENTAGE NORMOBLAST, GRANULOCYTES, LYMPHOCYTES, MONOCYTES AND PLASMA CELLS FROM STERNUM AND ILIUM. AVERAGE AND RANGE OF MAGAKARYOCYTES FROM SAME SITES

Sites	No. of Cases	Normoblasts %		Granulocytes %		Lymphocytes %		Monocytes %		Plasma Cells %		Megakaryocytes	
		Avg.	Range	Avg.	Range	Avg.	Range	Avg.	Range	Avg.	Range	Avg.	Range
Sternum	10	22.9	4.9–36.4	53	39.1–67	19.1	15.8–24	5.2	0.4–10.2	0.6	0.1–0.9	158	41–271
Iliac crest	22	25.5	9.3–36.7	46	32.3–70.6	22.7	11.2–35.2	5.1	0.4– 8.5	0.3	0.0–0.9	163	45–279

TABLE 3

RANGE IN PER CENT OF NORMOBLASTS, GRANULOCYTES, LYMPHOCYTES AND MONOCYTES FOUND ON DIFFERENTIAL COUNT IN PRESENT STUDY COMPARED TO REPORTS OF OTHERS

	Site and Technic	No. of Cases	Normoblasts %	Granulocytes %	Lymphocytes %	Monocytes %
Present Study	Sternum and ilium; volumetric, conc.	32	4.9 to 36.7	32.3 to 70.6	11.2 to 35.2	0.4 to 10.2
Diwany	Sternum; direct smear	10	5 to 18	60 to 89	12 to 27	0.4 to 3.0
Vogel and Bassin	Sternum; direct smear	41	4.5 to 38	38 to 83	1.0 to 30	—
Wolman*			12 to 25	—	5 to 35	—
Poncher	Sternum; direct smear from heparinized fluid	—	11 to 40	—	4 to 35	0 to 5

* From review of literature. Extreme of normal variation not represented.

Discussion

Wolman and Dickstein[6] reviewed the features of marrow examination which are of practical importance in clinical pediatrics and summarized trends noted by others[7,8] in the first few days of life. They found a high erythroid percentage (30 to 65%) at birth, which falls to a lower level (12 to 40%) by the seventh day. From an examination of chart 1, a similar trend is noted in this study. The five cases between 5 and 13 hours of age average 36% normoblasts, while the 15 hour to 6 day group averages 17% normoblasts. A reciprocal rise in granulocytes from 45 to 60% is noted in this study, similar to the trend recorded by Wolman and Dickstein.

In the previous report on the volumetric data from normal infants and children, it was noted that tibial aspirations in the older age group (2½ to 5 years) gave results that varied widely. There was, however, a general tendency for the data to reflect a relatively fatty and hypoplastic marrow with increasing age. In this study the differential cell counts reported from the tibial site likewise show marked variation in the older age range.

Numerous reports dealing with bone marrow in infants and children indicate that tibial aspirations performed on individuals up to 7 or 8 years of age continue to yield percentage cell distribution values comparable to those found from flat bones. With the technic used in this study, such a trend cannot be confirmed. The percentage of normoblasts may drop to less than 1% by 16 months of age (Case 27), and in half of the cases from 2 through 4 years of age less than 5% normoblasts were found. The majority of the cells were segmented granulocytes and lymphocytes. Similar findings are reported by Kramer and Hensch[9] in a study of tibial marrow from 41 infants, 14 days to 21 months old, in various states of health. They aspirated a small amount of marrow and made direct smears. The precise number, age and state of health of the cases that gave this result were not given; but they describe a marrow pattern difficult to distinguish from peripheral blood except for an occasional normoblast. Tecilazic[8] studied tibial bone marrow aspirated and prepared by similar technic in 35 normal infants 1 month to 2 years. He described similar findings on some occasions but attributed this to admixture with peripheral blood and repeated the aspiration.

It is difficult to explain, in the present study, this shift in the percentage distribution of cells from tibias of the 2 through 4 year old children on the basis of technic alone. In each instance similar technic was used in a study of these individuals' (Cases 31, 35 and 37) iliac crest marrow; and in these, as well as in the rest of the 22 cases 18 months through 4 years of age, no iliac aspirations produce the profoundly altered pattern noted from the tibias. In addition, the volumetric data from the tibias of these cases (see table 1 of previous report[1]) showed a low myeloid-erythroid and high fat layer. This altered cytologic pattern constitutes additional evidence indicating a difference in the normal anatomy of tibial marrow in the 2 through 4 year range compared to the sternal and iliac marrow. Furthermore, histologic study of gross particles removed from one of these cases revealed the marrow to be fatty and hypoplastic. Hence, it seems reasonable to anticipate that tibial aspirations from some normal individuals 1½ years of age or older will yield abundant fat, very low ME, a low-to-zero per cent normoblast, and a high per cent of segmented granulocytes and lymphocytes.

Sternum and Iliac Crest: With the volumetric technic employed in the study of marrow from the sternum and the iliac crest, the percentage distribution of major groups of cells falls within the range of normals reported by others.[6,7,10,11] Table 3 summarizes the range of percentage values for four major groups of cells reported by several investi-

gators[6,10-12] who aspirated small amounts from the sternum and used direct smear instead of concentration technics. The values found in the present study using a concentration technic are also listed. Except for the monocytes, the values appear to be quite comparable.

The high values found for monocytes in this study may be based on differences in interpretation of cells or in technic; this requires further investigation.

Conclusions

With the use of the described bone marrow aspiration and concentration (volumetric) technic, the percentage distribution of the major categories of cells appears to follow the general pattern reported from studies of bone marrow in infants and children by the direct smear technics.

The percentage distribution of nucleated cells from sternal and iliac aspirations in the age range studied showed no apparent differences between the two sites nor influence of age on the data.

In normal individuals as young as 1½ years of age and with advancing age thereafter, an increasing number of tibial aspirations show a very low percentage of normoblasts (0-5) and a majority of lymphocytes and segmented neutrophils.

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Spanish Abstract

Caracteristicas Volumetricas y Microscopicas de la Medula Osea de Niños Normales. II. Caracteristicas Citologicas

Se encontró que mediante el uso de la técnica de punción medular descrita y el metodo de concentración (volumetrico), la distribución de los porcentajes de las celulas principales de la medula ósea fueron en general semejantes a los observados en los estudios de la medula ósea de infantes y niños, mediante el uso de la tecnica directa de frotis de sangre.

Se observó que tanto en las punciones esternales como en las del hueso iliaco, el porcentaje de distribución de las celulas nucleadas fué similar en ambos sitios para el grupo de niños estudiados.

Se observó una baja notable en los porcentajes de normoblastos (0-5) con aumento de los linfocitos y neutrófilos, en las punciones de la tibia de niños normales de un año y medio de edad en adelante.

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ENDOCARDIAL SCLEROSIS

Review of Changing Concepts with Report of Six Cases

By HENRY W. EDMONDS, M.D.,* AND WALTER B. SEELYE, M.D.
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OBSERVATION has recently been made of a series of six cases of sudden death in infants in which hypertrophy of the left side of the heart, thickening, opacity and milky discoloration of the endocardium, and varying degrees of distortion of the cardiac valves were outstanding features at autopsy. The ages of these patients and the lack of evidence of postnatal infection or inflammation in the history, physical examination and necropsy suggest that these lesions may have been the result of an antenatal process, the nature of which is as yet not definitely established. Classically, cases of this type have been diagnosed as fetal endocarditis. More recently the term endocardial sclerosis, which the present authors prefer, has been proposed.

The pathogenesis is controversial, as manifest by the fact that there are almost as many variant opinions as there are papers written on the subject. If it could be proved that active inflammation can and does occur during the first two months of embryonic life, then many malformations of the heart might be ascribed to such a process. Whether the septal defects claimed to be associated with maternal rubella represent the results of localized inflammation or of an arrest of normal development conditioned by the inflammatory disease in the mother remains to be determined. According to Brown,[1] defective development or primary arrest before the eighth week of intrauterine life accounts for one group of congenital cardiac anomalies, while "infection" transmitted to the fetus from the mother after the second month, when the septa have closed, explains the remainder. The fallacy of establishing the first two months of embryonic life as the period during which inflammatory processes may not be damaging is apparent in the light of recent reports concerning the effect on the fetus of rubella in pregnancy.

Farber and Hubbard[2] in 1933 reviewed 10 cases collected from the literature and added four of their own in which the diagnosis of fetal endomyocarditis was based on gross and microscopic evidence pointing to old infection. They advanced the opinion that microscopic evidence of old inflammatory processes must include fibrosis, cellular infiltration and calcification in the underlying musculature. Thickening of the endocardium and distortion of the valves are the most important gross findings, valvular stenosis and atresia being the prevailing lesions.

Gross[3] in 1941 stated that "the myocardial lesions usually seen in so-called fetal endocarditis closely resemble healed bland infarcts" and suggested that such infarctions may result when arterioluminal, arteriosinusoidal and Thebesian vessels have been obliterated by fibrosis of the endocardium. He doubted that the occurrence of endocarditis in

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the fetus had ever been established and concluded that "the valvular and parietal endocardial changes seen in these cases are better explained on the basis of a developmental defect." Cosgrove and Kaump[4] also noted the resemblance of the myocardial lesions to infarcts and stressed the parallelism between the extent of myocardial and endocardial involvement. These authors preferred the term "endocardial sclerosis" and noted the variability of gross pathologic changes which include thickening and opacity of the endocardium in the simpler form, with distortion of the valves in the more severe instances. Focal necrosis with occasional calcification in the myocardium and large amounts of collagenous tissue in the endocardium are listed among their microscopic findings.

Sano and Anderson[5] presented a single case of the disease under discussion and commented on the marked hyperplasia of elastic tissue in the thickened endocardium. They concluded that the process "was developmental rather than infectious." Two cases of special interest because of their occurrence in siblings were reported by Weinberg and Himelfarb[6] under the diagnosis of "endocardial fibroelastosis," coined to emphasize this feature. The relation of the morphologic change of endocardial thickening to the functional changes of myocardial hypertrophy and ventricular dilatation, with resultant death of the infants, has been explained by these authors with reference to the work of Wearn[7] in a passage quoted as follows:

"Whatever the etiology of the endocardial fibro-elastosis, its presence can be used to explain the failure of the ventricle. With the development of such a thick fibro-elastic layer—one can well postulate some interference with the emptying of the arterio-luminal vessels into the ventricle because of constriction of their orifices by the elastic tissue. Thus, with the establishment of obstruction to the flow of blood, there would develop a dilatation of the intramyocardial capillaries, which would be accompanied by partial stasis of the blood stream. The myocardium would therefore be subject to some degree of anoxemia, which would be reflected in a dilatation and ultimate failure of the ventricle due to failure of the muscle to receive sufficient oxygenation for normal metabolism, and would be expected to interfere with normal contraction. This could conceivably result in death before histologic myocardial changes would have time to take place."

They believed that if this process went on long enough the myocardial alterations observed by Gross might well result. Wearn[7] demonstrated in clear anatomic detail the components of the coronary circuit which nourish the muscle walls of the heart. The arteriosinusoidal, arterioluminal and Thebesian vessels branch off directly from the coronary arterioles, traverse the atrial and ventricular wall and empty into the chambers. Mention is made of the possibility of a reversal of this flow "if the ostia of the coronary arteries are occluded" with subsequent change in the pressure relationships.

The present authors incline to the view that this work has taken the matter out of the field of speculation and has brought to light the most acceptable explanation yet offered of the myocardial changes associated with endocardial sclerosis and thickening, and has given a logical reason for the death of the infants here to be reported.

Case Reports

Case 1.—A male infant born at term was the second child of a healthy 28 yr. old mother. On the second day he became cyanotic and listless. A-radiograph showed slight enlargement of the heart with clear lung fields. A faint systolic murmur was heard over the precordium. Oxygen failed to relieve the cyanosis and the baby died early in the third day of life.

At necropsy, the heart was found to be enlarged, with both hypertrophy and dilatation more prominent in the L ventricle than in the R. (See Figs. 1 and 2.) The endocardium was cream-

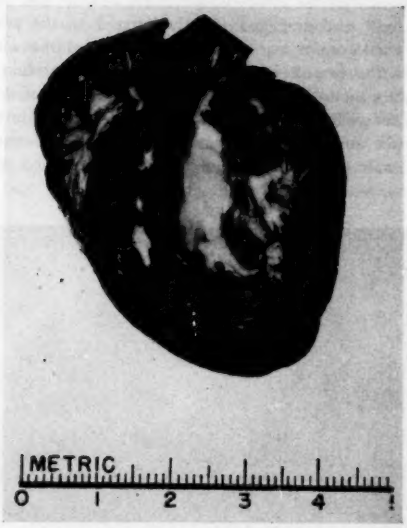

FIG. 1. Heart opened to show opaque, white, thickened endocardium lining L ventricle (endocardial sclerosis) and to show dilatation and hypertrophy of L ventricle. (Case 1.)

FIG. 2. Photomicrograph of lining of L ventricle of heart showing massive fibroelastic thickening of endocardium (endocardial sclerosis). Magnification ×48; elastica is stained black. (Case 1.)

colored and greatly thickened over the inner surface of the anterior and septal walls of the L ventricle, gradually becoming light pink-gray and slightly thinned on the posterolateral wall of the L ventricle. Elsewhere the endocardium was normal. The cusps of the aortic valve were thickened, rolled and indurated, with the free margins distorted into fleshy protuberances that almost met in the center, partially occluding the lumen. Other valve cusps were normal in form.

Microscopic section of the wall of the L ventricle showed marked fibrous thickening of the endocardium, especially over the surfaces of the papillary muscles. The myocardium was normal. In microscopic sections, the wall of the R ventricle appeared unchanged, while the aortic valve was thickened, and its normal tissue constituents irregularly arranged.

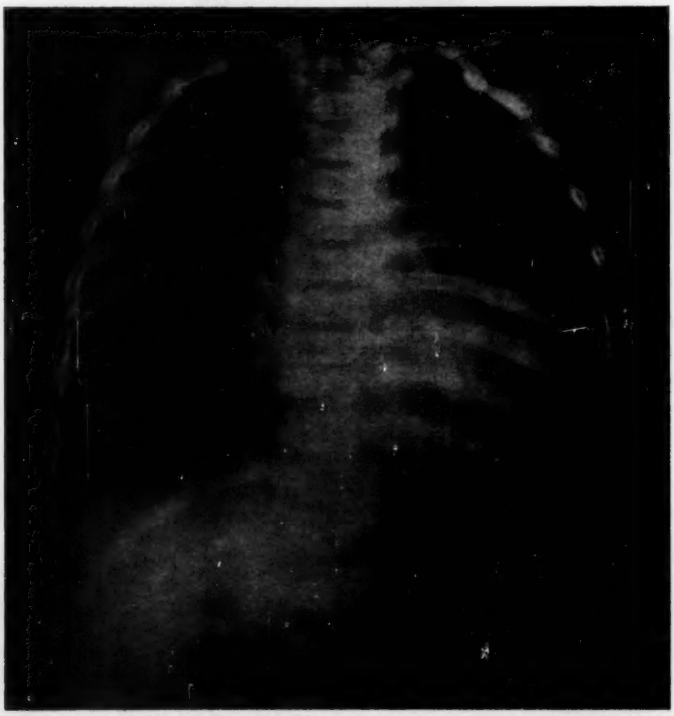

FIG. 3. Radiograph of chest showing enlargement of heart due to endocardial sclerosis. (Case 2.)

Case 2.—A male infant, born by normal delivery after an uncomplicated full term pregnancy, was the first child of a healthy 20 yr. old mother. At 10 days of age, cyanosis and irregular respirations were noted and "three doses of x-ray irradiation were given in treatment of an enlarged thymus." At 1 mo., another attack of cyanosis necessitated the administration of oxygen for 2 days. At 7 mo., he was admitted to the hospital with an upper respiratory infection. The skin was a diffuse, bluish, dusky color, respirations were rapid and marked retraction was observed in the supraclavicular region and in the intercostal spaces. There was a loud, blowing systolic murmur. In the roentgenogram the shadow of the heart was greatly enlarged, obscuring the lung markings at the L base. (See Fig. 3.) The baby was discharged at the end of 1 wk., having completely recovered from the respiratory infection. He was readmitted 5 wk. later, acutely ill, moderately dehydrated, with rapid grunting respirations accompanied by retraction of the lower half of the thoracic cage. The veins of the neck were dilated and the heart murmur had not changed in character. Temperature was 39.4° C. Penicillin and sulfathiazole were given and oxygen was supplied continuously. Cyanosis and difficult respirations persisted and death occurred on the third hospital day.

The heart was enlarged and globular, with some dilatation and moderate hypertrophy of the L ventricle. (See Fig. 4.) The myocardium was firm and light brown. The endocardium was normally translucent and inconspicuous throughout the R atrium and ventricle, whereas in the L ventricle it was opaque, gray-white and thickened. The aortic valve had only 2 cusps, which were delicate and well formed. The orifices of the 2 coronary arteries opened into the same sinus of Valsalva. The aortic ring was relatively somewhat smaller than the pulmonic ring. The descending limb of the arch of the aorta was sharply reduced to a diameter of 0.5 cm. at the level of the insertion of the ductus arteriosus. Below this point the caliber of the descending thoracic aorta was normal (1.0 cm.). The branches of the pulmonic trunk and of the arch of the aorta had the usual pattern.

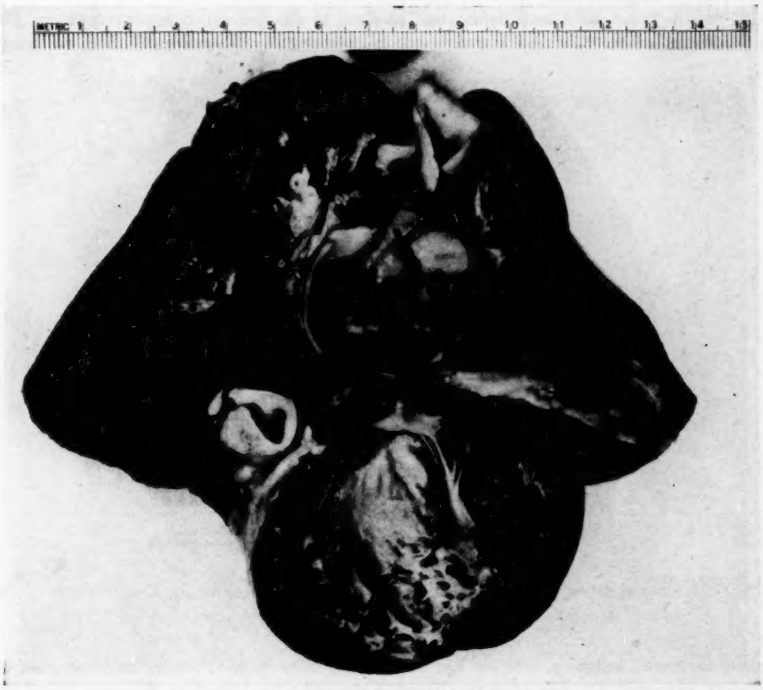

FIG. 4. Opened heart and lungs showing opaque, white, thickened endocardium lining L ventricle (endocardial sclerosis) and showing hypertrophy and dilatation of L ventricle. (Case 2.)

Microscopic sections of the heart showed marked thickening of the endocardium lining the walls of the L atrium and the L ventricle. This layer consisted of collagenous fibers densely packed together, with scattered fibroblasts and occasional monocytes. The demarcation between endocardium and myocardium was fairly sharp in the L atrium, but in the wall of the L ventricle there was extension of fibrosis in among the muscle bundles immediately underlying the endocardium, particularly prominent within the papillary muscles. Slight fibrous thickening of the mitral valve was apparent. A small patch of atheroma was present in the intima of a large branch of the coronary arteries situated within the atrioventricular sulcus.

Case 3.—A full term female infant, the fourth child of healthy parents in their early thirties, was delivered normally after an uneventful pregnancy. The siblings were all living and well. On examination at 6 wk. no abnormalities were found and the heart tones were normal. At 2 mo. a dry cough developed. A radiograph showed widening of the aortic and cardiac shadow, almost completely obscuring the L lung. The cough persisted and transitory blue spells occurred. Two weeks later the baby was found dead in her crib.

At postmortem examination, the heart was enlarged to a weight of 90 gm. (23 gm. is normal for this age). The apex was rounded, giving the heart a globular shape. There was moderate dilatation of the L ventricle, with slight deflection of the interventricular septum toward the right. The endocardium lining the L ventricle was slightly thickened and semi-opaque; elsewhere it was not altered. The chordae tendineae of the mitral valve were markedly shortened. The free margins of both cusps were rolled and thickened, resulting in slight shrinkage of the cusps. The other valves were delicate and well formed.

Two sections of myocardium including portions of the wall of the L ventricle and L atrium showed well preserved, essentially normal myocardium bordered on the endocardial surface by a thick layer of collagen bundles.

Case 4.—A 7 mo. old female infant was admitted to the hospital in acute respiratory distress. The mother stated the baby had had difficulty in breathing for the past week. She was born pre-

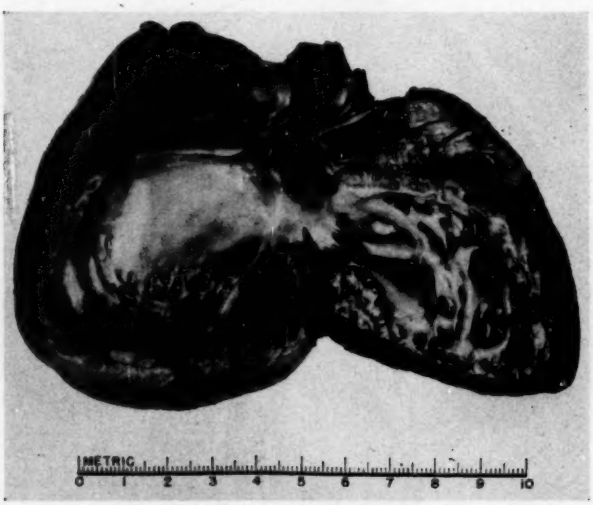

FIG. 5. Heart opened to show opaque, white, thickened endocardium lining L ventricle (endocardial sclerosis) and to show dilatation and hypertrophy of L ventricle. (Case 5.)

maturely at 7 mo., weighing only 1.3 kg., but she had been in good health until the onset of the respiratory symptoms. On admission the diagnosis was asthmatic bronchitis. Measures to relieve distress included administration of epinephrine and oxygen, and sedation. She died early the next day, 12 hr. after admission.

At necropsy, the heart weighed 89 gm. (34 gm. is average for 7 mo.) and was globular. The cavity of the L ventricle was dilated with blunting of the apex and deflection of the interventricular septum toward the right. The thickness of the myocardium averaged 0.4 cm. in the wall of the R ventricle and 1 cm. in the wall of the L ventricle. The foramen ovale was closed. The endocardium was opaque, pearly gray, and thickened over the septal wall of the L ventricle, shading off into slightly thinned endocardium over the lateral wall of the L ventricle and over the L atrium. The endocardium in both chambers of the R side of the heart was normal.

Microscopically, a section though the wall of the L ventricle disclosed moderate fibrosis of the endocardium with thickening. The myocardium appeared normal.

Case 5.—A female infant was admitted to the hospital at 1 yr. of age because of failure to gain weight for the past 9 mo. and gasping respirations for most of her life, and with the signs of an acute respiratory infection. She had had "pneumonia" 3 mo. before with uneventful recovery. There was moderate cyanosis. No heart murmurs were heard. She died during the night in acute respiratory distress.

At necropsy the heart was tremendously enlarged but essentially normal in shape. The endo-

cardium throughout the surface of the L ventricle and L atrium was opaque, pale gray-white and thickened to an average of 0.1 cm. (See Fig. 5.) This endocardium was tough and inelastic when cut. The cusps of the mitral valve were thickened, resembling the endocardium. The mitral orifice was somewhat narrowed. Other valve cusps and rings were normal.

Microscopic examination of sections through the L atrium, L ventricle and mitral valve all showed marked endocardial thickening with fibrosis. (See Fig. 6.) The myocardium was not remarkable.

Case 6.—A full term male infant had had otitis media at 9 mo. At 18 mo., swelling of hands, feet and face was noted. The baby was treated at another hospital with digitalis. On admission to Children's Orthopedic Hospital at 19 mo., there was generalized edema, abdominal distention and pallor. The heart was enlarged but there were no murmurs. The liver was palpable 5 fingerbreadths below the costal margin. A radiograph showed increased heart size with preponderance of the enlargement on the left and passive congestion. An electrocardiogram gave evidence of mild cardiac

FIG. 6. Photomicrograph of lining of L ventricle of heart showing massive fibroelastic thickening of endocardium (endocardial sclerosis). Magnification ×48; elastica is stained black. (Case 5.)

damage with digitalis effect. The child was discharged improved at the end of a week, but a month later he was rushed back to the hospital in extremis. He was dead on arrival.

At necropsy, the heart and lungs together weighed 380 gm. (200 gm. is average combined weight for 18 mo.). The heart was moderately enlarged, owing principally to dilatation of the L ventricle. The pericardial surface was normal. The great vessels, arterial and venous, had normal arrangement and pattern of branching. The ductus arteriosus and the foramen ovale were closed. The endocardium was normally pale and translucent in the R atrium and ventricle. It was slightly opaque and thickened over the L lateral surface of the muscular interventricular septum, very slightly opaque over the postero-lateral walls of the L ventricle and greatly thickened, opaque and cream-colored throughout the L atrium. There was dilatation of both the L atrium and L ventricle. The myocardium was pale and of normal texture in the R ventricle. In the walls of the L ventricle there were poorly defined, firm, light gray-pink fibrous areas, shrinking slightly beneath the level of the cut surface. The coronary arteries arose in the usual manner and had the normal pattern of branching. The interventricular septum was intact. There was slight thickening of the mitral valve cusps without narrowing of the orifice. Other valve cusps were normal in form.

Discussion

The six cases here presented seem notably similar in respect both to clinical and pathologic features. Following a story of relatively mild symptoms of cardiac malfunction in infancy, usually with radiographic demonstration of heart enlargement and with finding of nondescript murmurs (generally systolic), the patients have died suddenly. In only one case has there been evidence of congestive heart failure. Deformity of the mitral or aortic cusps has been fairly constant, characterized by thickening of cusps, with rolling of the free margins and (in the case of mitral involvement) with similar deformity of the attached tendinous chords. The affected valves appeared mildly stenotic. The enlargement of these hearts seemed out of proportion to the valvular deformity, explainable only on the basis of intramyocardial congestion provoked by the occlusion of capillary drainage into the ventricle.

The most striking anatomic feature has been moderate to marked thickening of the mural endocardium, generally best developed over the anteroseptal surface of the left ventricle, but sometimes involving the entire left ventricle and the left atrium as well. Microscopic examination of the affected areas has demonstrated dense collagenous-fibrous tissue in lieu of normal endocardium, obviously a change of considerable duration, and possibly referable to the time of the actual formation of the heart. Microscopic sections have failed to disclose Aschoff bodies of rheumatic carditis, "Bracht-Waechter" bodies of bacterial carditis, the myocardial inclusions of toxoplasmosis, or indeed any definite abnormality of the muscle. Microscopically the affected valves have appeared simply thickened and not otherwise abnormal.

The diagnosis of "fetal endocarditis" has been applied to cases such as these in the past. While this diagnosis has been a convenient one, it should be discouraged because of its unwarranted implication of an inflammatory pathogenesis. That the lesions may have been the result of primary maldevelopment seems more likely than that they resulted from an inflammatory distortion of tissue differentiation. In either case an antenatal origin of the processes is assumed because of the youth of the patients in comparison with the age of their lesions.

As a group these cases may represent a distinct species of congenital cardiac malformation, perhaps analogous to the group of transpositions of the great arterial trunks of the heart. The various froms of transpositions have been grouped together on the basis of a theoretic common denominator—incomplete or arrested torsion of the primitive bulboventricular loop of the heart in the early embryo. Perhaps cases of left-sided endocardial thickening with valve deformity, such as here presented, may find a theoretic common denominator in terms of segmental variation in tissue differentiation. Extensive fibroelastosis in the truncus segment of the embryo produces normally differentiated aortic and pulmonic trunks. Similar but less pronounced fibroelastosis in a portion of the bulboventricular loop would represent heterotopia resulting in the lesions of endocardial sclerosis.

Conclusion

Six cases of heart disease have been presented, with a hint that they may be type specimens for a distinct species of congenital cardiac malformation. They are representative of a syndrome characterized pathologically by hypertrophy of the left side of the heart, thickening of the mural endocardium of the left ventricle, and varying distortion of the aortic and mitral valves, and characterized clinically by radiologically demonstrable

cardiac enlargement, nondiagnostic murmurs and sudden death in infancy. The older concept of an inflammatory pathogenesis of so-called "fetal endocarditis" is rejected in favor of developmental origin of the lesions.

Note

During the final revision of this paper for publication, there appeared a recent study[8] from Farber's laboratory, substantially retracting Farber's earlier support[2] of an inflammatory pathogenesis of lesions of the type here discussed and favoring a developmental origin.

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Spanish Abstract

Esclerosis Endocardica; Revisión de los Conceptos Actuales y Reporte de Seis Casos

Se reportan seis casos de un sindrome cardiaco caracterizado patologicamente por una hipertrofia cardiaca izquierda, hipertrofia de la zona mural del endocardio del ventriculo izquierdo, y alteraciones variables de las valvulas mitral y aortica. Clinicamente éste sindrome se caracteriza por la demonstración radiologica de una cardiomegalia, soplos cardiacos sin valor diagnostico, y muerte repentina en la infancia. Los autores rechazan el concepto inflamatorio (endocarditis fetal), por el de un defecto del desarrollo como causa de estas lesiones.

Children's Orthopedic Hospital

TRICUSPID ATRESIA

Report of Three Cases and Evaluation of Diagnostic Criteria

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CONGENITAL tricuspid atresia or stenosis is a cardiac anomaly in which there is absence of normal communication between the right auricle and the right ventricle and failure of development of the right ventricle. It is this failure of normal development of the right ventricle which should provide the clues leading to the antemortem recognition of tricuspid atresia. The diagnostic criteria are stated to be: persistent cyanosis, a concave left upper cardiac border in the anterior-posterior roentgenogram, absence of right ventricular enlargement in the left anterior-oblique projection, and the substantiating electrocardiographic picture of left axis deviation.

Tricuspid atresia is one of the cyanotic forms of congenital heart disease which may be alleviated by providing additional pulmonary blood flow.[1,2] The majority of infants with this anomaly die before the age at which the Blalock-Taussig operation is generally advised. It has been shown, however, by Gasul and his associates that the Potts-Gibson procedure is both feasible and effective in very young infants with tricuspid atresia.[3]

The possibility of surgical relief of very young infants with tricuspid atresia and the present authors' experience with this anomaly prompted a review of the more recent pertinent literature. Awareness of the limitations of the generally accepted diagnostic criteria for the clinical recognition of tricuspid atresia is desirable.

The literature of the past 17 years has been reviewed and 44 cases in which data were available have been analyzed.* In addition, three hitherto unreported cases of congenital tricuspid atresia or stenosis are presented, in one of which the roentgenologic and the electrocardiographic findings are noteworthy.

REVIEW OF THE LITERATURE

Incidence.—Grayzel and Tennant list 15 cases of tricuspid atresia reported prior to 1933. In a review of the literature since 1933, 57 additional cases were found, bringing the total to 72.[3-26]

Sex.—There was an equal distribution of males and females among the reported cases.

Age at Time of Death.—Age at time of death ranged from 6 days to 25 years in 26 cases in which it was noted. The average age was 2 years, 8 months, although the average dropped to 12 months if 2 patients (12 and 25 years old, respectively, at time of death) were excluded. Approximately one third of the patients died by the age of 6 months, and three fourths were dead before the age of 1 year.

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* Since this paper was completed, the following reference has been called to the authors' attention: Edwards, J. E., and Burchell, H. B., Congenital tricuspid atresia: Classification, M. Clin. North America 33:1177, 1949.

Pathologic Findings.— Autopsy data were available on 20 cases. Half of these had not only tricuspid atresia but complete atresia of the pulmonary orifice as well. Among the cases with associated pulmonary atresia, all had a patent ductus arteriosus; the ventricular septum was intact in all but two. In six of the remaining cases, the pulmonary artery was normal in size, an interventricular septal defect was present and the ductus arteriosus was closed. Three cases had hypoplastic pulmonary arteries, with stenosis at the infundibulum in one and stenosis at the valve in the other two. In 10 of the cases, the communication between the right and left auricle was stated to be a patent foramen ovale, and in six cases an interauricular septal defect was present.

In all cases the left ventricle was definitely enlarged. The right ventricle was hypoplastic or rudimentary in every case, although the thickness of the muscle wall of the right ventricle was stated to be normal in some. In six cases, transposition of the great vessels was present.

Clinical Findings.—Cyanosis was generally present at birth and persistent, although in a few cases it was not noted until after the neonatal period. Clubbing was present in 13 cases. Dyspnea was marked either at rest or paroxysmally in some of the patients. The lungs were clear in all patients except three, in whom scattered rales were heard preterminally. Retarded physical growth was common.

Murmurs diagnostic of tricuspid atresia have not been described. Murmurs were present in 20 of 28 patients in whom their occurrence was specifically mentioned. The murmurs were systolic in all, and in one case there was also a diastolic murmur. They were usually loud, and maximal to the left of the sternum from the second to the fourth interspace. The heart was clinically enlarged in seven patients. The liver was palpable in six patients, but in only one of these was any definite pulsation stated to be present.

The hemoglobin level ranged from 14 to 29 gm./100 cc., with an average of 19 gm. The red blood cell count ranged from 5 to 12 million/cmm., with an average of 7 million.

Electrocardiographic Findings.—Among the cases reviewed, electrocardiograms were obtained in 39. Left axis deviation was present in 36 of these cases. In three patients, 10 weeks old, 7 months old and 11 months old, respectively, no axis deviation was found.[24–26] In one of the three cases without axis deviation, unipolar leads were utilized and these were thought to show hypertrophy of both ventricles.

Roentgenologic Findings.—In 33 of the cases reviewed, RGs were obtained. Films were reproduced in 23 of these cases, and the findings were mentioned briefly in an additional 10.

A. Postero-anterior view.—In most cases, the heart was either normal in size or only slightly enlarged. The apex of the heart was usually slightly elevated, but the elevation of the apex was usually not as striking as that found in the tetralogy of Fallot. Furthermore, there was usually greater fullness of the lower left (left ventricular) cardiac border than is commonly seen in the tetralogy of Fallot. A moderate concavity of the pulmonary artery segment of the left upper cardiac border was noted. The pulmonary vascular markings were usually either diminished slightly or at the lower limits of normal. In some cases, the presence of diminished blood flow to the lungs could not have been definitely stated on the basis of the RGs. The "characteristic fine, mottled and reticulated pattern" in the lungs due to bronchial arterial anastomoses[27] was not a prominent roentgenologic feature in the reported cases.

Taussig[13] states that in tricuspid atresia the great vessel shadow is usually narrow in the

frontal projection. Neuhauser,[27] however, has commented that the aortic shadow is often somewhat enlarged. In about one third of the reported cases, the presence of a narrow mediastinal shadow was mentioned. In general, this does not appear to be an important diagnostic feature.

B. Left anterior-oblique view.—Taussig has stressed the fact that the presence of a small or rudimentary right ventricle is suggested by failure of the heart border to project significantly anterior to the aortic shadow in the left anterior oblique view. She has pointed out that the left ventricular enlargement in this anomaly is expressed by the posterior displacement of the posterior cardiac border. In the reported cases, the left anterior oblique view was not utilized sufficiently to permit any definite conclusions.

C. Other views.—The right oblique view is not helpful in establishing the diagnosis. In at least one case of proved tricuspid atresia, the statement was made that at fluoroscopy the heart in the right anterior oblique view projected forward into what was considered the region of the right ventricle. The lateral view was not utilized in a sufficient number of cases to be evaluated.

Thus, except for the fact that the apex is somewhat lower and that there is somewhat greater fullness of the left lower (left ventricular) cardiac border in the frontal projection, the roentgenographic appearance of tricuspid atresia in the postero-anterior view need not be strikingly dissimilar from that of the tetralogy of Fallot. The left anterior oblique view may give adequate evidence of the enlarged left ventricle and of absence of enlargement of the right ventricle.

D. Angiocardiography.—Brown[24] and Cooley et al.[26] have reported angiocardiographic studies of tricuspid atresia in the frontal, oblique and lateral projections. With adequate studies, the diagnosis should be made by the observation of sequential opacification of the right auricle, the left auricle and the left ventricle. Cooley et al.[26] have pointed out that the three findings of significance are: 1. The demonstration of a communication between the auricles, best shown in the frontal projection. 2. Nonvisualization of the right ventricle, or visualization of the small right ventricle, best shown in the lateral projection. 3. The demonstration of a large left ventricle, seen equally well in the frontal or lateral projections.

Cardiac Catheterization.—Studies with intracardiac catheterization are not conclusive, although they may be highly suggestive. They demonstrate the presence of an interauricular septal defect and inability to catheterize the right ventricle.[20]

Case Reports

Case 1. E.G.: A 5 wk. old female infant was cyanotic at birth. Feedings were taken poorly and she steadily lost weight until she was hospitalized at the age of 5 wk. Examination showed a cyanotic, poorly nourished infant. Cyanosis increased with crying. Heart was enlarged to percussion. No murmurs were heard. Lungs were clear. Liver edge was palpable at the level of the umbilicus and did not pulsate. Hgb. was 17 gm./100 cc. Electrocardiographic studies showed no axis deviation. Unipolar leads gave no evidence of L ventricular hypertrophy. Routine roentgenologic examination, including films and fluoroscopy, showed the heart to be massively enlarged in the P-A view (Fig. 1). Supracardiac vascular pedicle was narrow, but failed to widen in the LAO view (Fig. 2). Heart border extended well anterior to the aortic shadow in the LAO view and in the lateral view (Fig. 3), and there was thought to be marked R auricular enlargement and probably R ventricular enlargement as well. In addition, in the L oblique view, the posterior cardiac border projected far posteriorly, indicating L ventricular enlargement. Lung fields were abnormally clear.

Angiocardiography, performed with 10 cc. of 35% diodrast® injected into the R femoral vein, demonstrated the inferior vena cava up to its point of junction with the heart on the initial film.

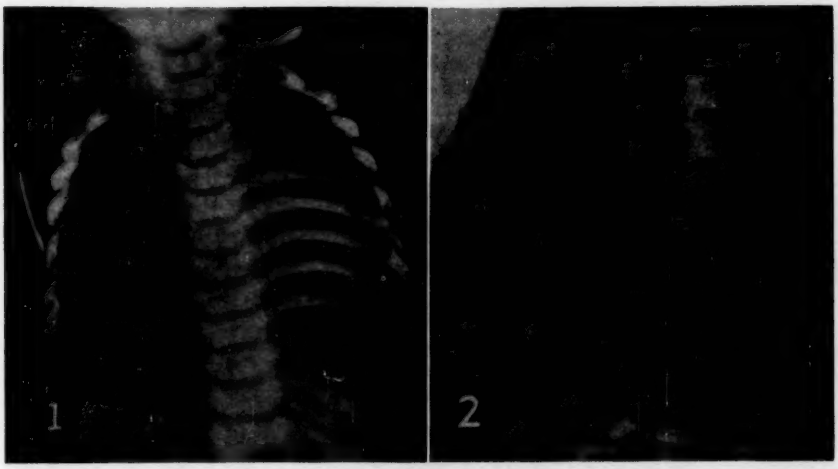

FIG. 1. Case 1. P-A view. Heart is massively enlarged. Lung fields are abnormally clear. Great vessel shadow is narrow.

FIG. 2. Case 1. LAO view. Anterior heart border bulges anteriorly. Posterior heart border projects behind spine.

On the second film, taken at approximately 2 sec., the L side of the heart, including the L auricle and L ventricle, was well opacified (Fig. 4). The aorta also was visualized. These findings suggested the possibility that the inferior vena cava emptied into the L auricle. Review of the films, however, revealed minimal opacification in the region of the R auricle, suggesting the presence of tricuspid atresia.

The patient's condition remained poor and she died 4 days after admission. Autopsy disclosed tricuspid atresia, a large atrial septal defect, pulmonary atresia and a patent ductus arteriosus (Fig. 5). The R ventricular wall was of normal thickness but the R ventricular cavity was essentially an

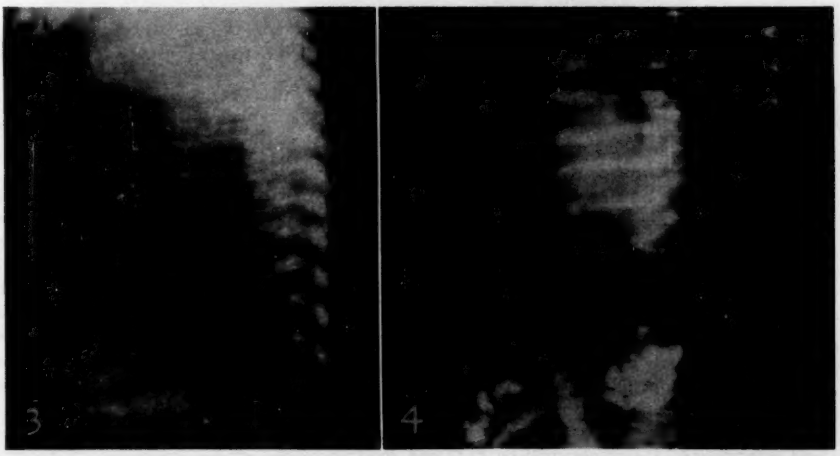

FIG. 3. Case 1. L lateral view. Anterior heart border projects forward prominently.

FIG. 4. Case 1. Angiocardiogram at 2 sec. LAO view. Opacification of inferior vena cava and L side of heart is clearly seen. Aorta is visualized.

endothelial-lined slit. Main pulmonary artery was an atretic band. Lungs received their blood supply through the patent ductus, which communicated with small right and left pulmonary arteries.

Comment: This case presented the problem of a markedly incapacitated cyanotic infant, with massive cardiac enlargement. ECG showed no axis deviation and unipolar leads failed to establish the presence of L ventricular hypertrophy. In the LAO oblique view, the cardiac border projected significantly anterior to the aorta, and the posterior cardiac border projected posterior to the spine. Initially the possibility of transposition of the great vessels was considered, but at fluoroscopy the vessel shadow in the LAO view was markedly narrow and distant from the anterior chest wall. The angiocardiogram which demonstrated almost immediate filling of the L heart and aorta, further eliminated the possibility of transposition.

FIG. 5. Case 1. Autopsy specimen in situ. Anterior view. R. A., right auricle. L. V., left ventricle.

Case 2. S.H.: An infant was first seen at the age of 4 mo. because of persistent cyanosis since birth. On physical examination, marked cyanosis was noted and clubbing of thumbs and toes was already present. Lung fields were clear. A high-pitched blowing systolic murmur was heard over the entire precordium. Liver, 4 finger-breadths below the costal margin, did not pulsate. Hgb. was 20 gm./100 cc. and RBC count was 9.5 million cmm. ECG showed L axis deviation. Roentgenologic examination showed minimal cardiac enlargement, a concave pulmonary artery segment and slight elevation of the apex in the frontal projection (Fig. 6). There was fullness of the L lower cardiac border. In the LAO view, there was continuity of the R ventricular contour and the aortic shadow producing a relatively flat anterior border (Fig. 7). This suggested the presence of a small R ventricle. A Pott's operation, performed on the child at the age of 1 yr., was followed by marked improvement. This improvement persisted, and he is alive and relatively well at the age of 3 yr.

Comment: This case illustrates the classical findings in tricuspid atresia: persistent marked cyanosis and polycythemia, L axis deviation on ECG and roentgenographic studies suggesting the presence of a small R ventricle and L ventricular enlargement.

Case 3. R.H.: A 6 mo. old boy had been cyanotic since about 24 hr. after birth. At that time

RGs were made and the diagnosis of a congenital cardiac anomaly of undetermined type was made. Following discharge from the nursery, cyanosis persisted. Severe dyspnea was associated with crying and feeding. He was admitted to the hospital at the age of 6 mo. Physical examination showed generalized deep cyanosis and a variable systolic murmur heard best in the region of the R nipple. Liver was palpable 2 fingerbreaths below the costal margin. Clubbing of fingers and toes was present. At that time he had an RBC count of 9.3 million/cmm. and Hgb. of 16 gm./100 cc. ECG was consistent with dextrocardia but evidence of R ventricular hypertrophy was not noted. Roentgenologic examination demonstrated the presence of dextrocardia, moderately avascular lung fields and a

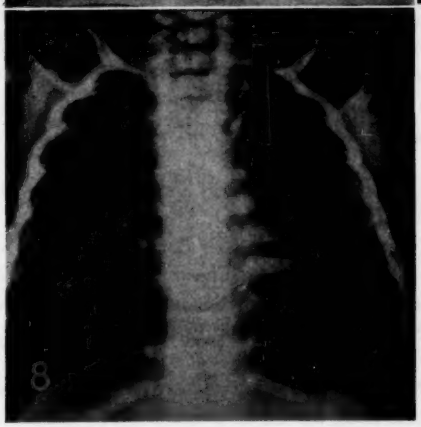

FIG. 6. Case 2. P-A view. Pulmonary artery segment is concave. Note fullness of lower L cardiac border, with slight elevation of apex of heart.

FIG. 7. Case 2. LAO view. R ventricular border fails to project anterior to aorta. This suggests presence of small R ventricle.

FIG. 8. Case 3. P-A view. RG has been reversed for purposes of comparison. Dextrocardia, however, was present. Lung fields are clear, pulmonary artery segment concave, and heart normal in size.

concave pulmonary artery segment (Fig. 8). He was thought to be too poor a risk for operation and was discharged unimproved. He died at about 7 mo. of age. In addition to the dextrocardia, autopsy revealed hypoplasia of tricuspid orifice, pulmonary artery atresia and a hypoplastic R ventricle. Foramen ovale was patent and a patent ductus arteriosus carried the blood from the aorta into the R and L pulmonary arteries. There was massive left ventricular enlargement.

Comment: Roentgenologic findings on this child were those of dextrocardia, clear lung fields, a concave pulmonary artery segment and elevation of the apex of the heart. Electrocardiographic findings, complicated by the dextrocardia, failed to clarify the nature of the anomaly. Angiocardiography might have established the diagnosis but was not used since the child was considered too poor a surgical risk.

Discussion

Routine clinical, roentgenographic and electrocardiographic studies are usually sufficient to establish the diagnosis of tricuspid atresia. A definite pre-operative diagnosis may depend, however, on additional studies.

The blood flow in tricuspid atresia is from the right auricle to the left auricle through either an interauricular septal defect or a patent foramen ovale and thence to the left ventricle. From the left ventricle the pulmonary circulation may be supplied in three ways: (1) if an interventricular septal defect is present the blood may pass through a rudimentary right ventricle to a pulmonary artery which is either hypoplastic or normal in size; (2) the pulmonary artery, however, may be atretic, or the ventricular septum intact, and then the pulmonary flow is by way of a patent ductus arteriosus or (3) the bronchial arteries.

These different pathways may produce variations in the clinical and roentgen manifestations. Thus, if the opening between the auricles is small, there may be hepatic enlargement and a presystolic pulsation of the liver margin. In general, however, the physical findings in tricuspid atresia do not distinguish this malformation from others of the cyanotic group. Differential diagnosis depends on the electrocardiographic and roentgenologic findings.

Electrocardiographic Findings.—The statement has been made frequently that tricuspid atresia is the only congenital cardiac malformation in the cyanotic group with associated left axis deviation.[14,15,17–19] In 1939 Ash et al.[28] reported a patient with transposition of the great vessels whose ECG showed left axis deviation. A child with the tetralogy of Fallot and left axis deviation on ECG has been described by Gasul and associates.[29] Sokolow and Edgar,[30] in a study of unipolar ECGs in congenital heart disease, found six cyanotic cases with left axis deviation or left ventricular hypertrophy. Three of these had tricuspid atresia, while one had a truncus arteriosus and a patent ductus arteriosus, and the remaining two had the tetralogy of Fallot with associated patent ductus arteriosus.

It is apparent, then, that the presence of left axis deviation in a cyanotic child with congenital heart disease need not be diagnostic of tricuspid atresia.

Conversely, tricuspid atresia need not always manifest left axis deviation. Taussig in 1947 pointed out that no axis deviation may be seen in very young infants with tricuspid atresia. Of the three cases of tricuspid atresia without left axis deviation reported in the literature, none was in a very young infant. The present authors' Patient E.G., however, was 7 weeks of age.

Thus, although left axis deviation usually is manifest relatively early, it may not be apparent as late as 11 months of age. In these cases, the use of unipolar precordial leads may show left ventricular hypertrophy. The use of unipolar precordial electrocardiographic study in the cyanotic congenital cardiac defects is of further importance in that this may show the presence of left ventricular hypertrophy in vertical hearts showing right axis deviation in the standard leads.[31]

Roentgenologic Findings.—Classically the heart is normal in size or but slightly enlarged in the frontal projection. The appearance may resemble that of the tetralogy of Fallot except for the presence of slightly greater fullness of the left lower cardiac border and less elevation of the apex because of the enlarged left ventricle. The pulmonary artery segment is concave. The lung fields are relatively avascular. In the left anterior

oblique view, the straightened anterior border suggests the absence of right ventricular enlargement. These findings are illustrated by Case 2.

That the classical roentgenologic findings are not always present is clearly demonstrated by Case 1. The heart was massively enlarged in all projections. The pulmonary artery segment was not concave. Indeed, the configuration of the heart in the postero-anterior view resembled that of transposition of the great vessels, with a strikingly narrow great vessel shadow. The great vessel shadow, however, failed to widen in the left anterior oblique view at fluoroscopy. This, in conjunction with the clear lung fields, made transposition an unlikely possibility. In the left anterior oblique view, not only was there no straightening of the anterior heart border, but it extended far anterior to the root of the aorta. Although it was thought that this represented in part an enlarged right auricle, the presence of right ventricular enlargement was suspected. The prominent extension of the posterior heart border behind the spine strongly suggested an enlarged left ventricle.

The portion of the heart projecting anterior to the aorta was shown at autopsy to be an enlarged right auricle and the hypoplastic right ventricle. Thus, the prominence of the anterior heart border in relation to the ascending aorta proved to be misleading. This sign may be further misleading in that failure of the right ventricular shadow to project anterior to the aorta may also be noted in congenital cardiac anomalies in which right ventricular enlargement is present. When the aorta is anteriorly placed as in complete transposition of the great vessels, or in the presence of a right-sided aorta or of a dextraposed aorta, there may be smooth continuity of the aortic and right ventricular shadow, forming a relatively straight anterior border in the left anterior oblique view. In such situations, the chamber size of the right ventricle becomes more difficult to assess in this projection.

Angiocardiography is most useful in those cases which are atypical and in which the diagnosis is obscure. In Case 1, the region of the right ventricle was never opacified. The fact that the right auricle did not appear to opacify significantly brought up the possibility of drainage of the inferior vena cava into the left auricle. Review of the films revealed the presence of early faint right auricular opacification and suggested the diagnosis of tricuspid atresia.

Conclusion

Because the antemortem diagnosis of tricuspid atresia may lead to corrective cardiac surgery, the criteria for diagnosis—and their limitations—must be clearly delineated. In most cases the classical findings will lead to an unequivocal diagnosis. But it must be recognized that the combination of a congenital cardiac anomaly of the cyanotic type with left axis deviation is by no means pathognomonic of tricuspid atresia. Conversely, the absence of left axis deviation on the ECG does not exclude the possibility of tricuspid atresia. Similarly, roentgenologic studies need not be conclusive. The presence of an underdeveloped right ventricle may be obscured in the conventional examination. In atypical cases, angiocardiography may be the only method of establishing the diagnosis conclusively.

For the intensely cyanotic young infant whose immediate prognosis is poor, special diagnostic procedures should be performed whenever conventional methods have failed to clarify the nature of the anomaly. Although some risk is attached to these procedures,[32] the danger may be far less than in conservative management of such cases.

SUMMARY

The recent literature on congenital tricuspid atresia is reviewed. Three previously unreported cases are described. The generally accepted diagnostic criteria are discussed and elaborated.

ACKNOWLEDGMENT

Dr. Ann Purdy permitted the inclusion of Cases 2 and 3.

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SPANISH ABSTRACT

Atresia Tricuspidea: Reporte de Tres Casos y Evaluación del Criterio Diagnóstico

La atresia o estenosis tricuspidea es una cardiopatía congenita de tipo cianotico, la cual puede ser aliviada mediante el establecimiento de una comunicacion entre la circulación pulmonar y la circulación general. Esta cardiopatía generalmente se caracteriza por la presencia de una cianosis persistente desde el nacimiento, la ocurrencia de soplos sistolicos sin valor diagnostico, aumento de la hemoglobina, desviación hacia la izquierda del eje del electrocardiograma, y evidencia radiologica de la presencia de un ventriculo derecho pequeño y aumento de tamaño del ventriculo izquierdo. El exámen angiocardiografico demuestra la opacificación progresiva de la auricula derecha, auricula izquierda y ventriculo izquierdo, con ausencia de opacificacion significante del ventriculo derecho.

Los autores reportan tres casos de atresia o estenosis tricuspidea congenita, uno de los cuales se caracterizó por la ausencia de la desviacion hacia la izquierda del eje del electrocardiograma y presencia de signos radiologicos aparentemente consistentes con un aumento de tamaño del ventriculo derecho. En este caso, sin embargo, el examen angiocardiografico indicó el diagnóstico de atresia tricuspidea.

Los autores estiman que la asociación de cardiopatías congenitas de tipo cianotico con desviación hacia la izquierda del eje del electrocardiograma, no es patognomonico de una atresia tricuspidea, ya que dicha combinación puede presentarse en otras cardiopatías congenitas tales como: la transposición de los grandes vasos, truncus arteriosus, tetralogia de Fallot con comunicación intrauricular, y en la tetralogia de Fallot con persistencia del conducto arterioso. Viceversa, la presencia de una desviación hacia la izquierda del eje del electrocardiograma no siempre ocurre en todos los casos de atresia tricuspidea. Similarmente, se señala que a veces el exámen radiologico de rutina no demuestra la presencia de un ventriculo derecho pequeño. Se sugiere un examen angicardiografico en casos dudosos como el unico metodo de diagnóstico eficaz.

Clay and Webster Streets

AURICULOTEMPORAL SYNDROME

Report of a Case Developing in Early Childhood with a Review of the Literature

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INJURY to the parotid gland area is occasionally followed by flushing and sweating of the ipsilateral cheek whenever the patient eats. In these patients the injury has for the most part produced anatomic division of the tissues involved and has usually consisted of a suppurative parotitis or surgical interference in the parotid area. Since the cutaneous changes occur in the distribution of the auriculotemporal nerve and are apparently mediated by that nerve, the syndrome has been termed the auriculotemporal syndrome. The incidence has not been clearly demonstrated, but it has been described in the literature about one hundred times[1-26] and is seen with some regularity in large clinics where parotid surgery is frequently performed.[1] The condition has seldom been reported in children, and has not been adequately described in the English pediatric literature. The following case is reported in order to bring this symptom-complex to the attention of pediatricians.

CASE REPORT

A. P. (#A240570) was first seen at the Children's Medical Center at the age of 23 days with bilateral Staph. aureus abscesses of the lateral aspect of the neck and parotid areas of 10 days' duration. Incision and drainage was performed on both sides following the line of the mandible at the angle of the jaw and on the left side below the jaw. A questionable mild facial palsy was evident for a few days but the infection gradually subsided and the infant was considered completely well after 3 mo. of age.

Sometime during the second year of life the patient's family first noted flushing of both cheeks brought on by eating. Sweating first appeared with the flushing at about 5 yr. of age; since then, both flushing and sweating occur at each meal. There have never been any subjective components to the reaction. A bright red erythema is seen over both cheeks within 30 sec. after the beginning of mastication of any food. This is followed within another 30 sec. by tiny beads of sweat in the same area. The reaction persists as long as the boy continues to eat and fades within 3 or 4 min. after the end of the meal. In cold weather strenuous exercise alone, without eating, may produce the reaction; in the summer, exercise is not a sufficient stimulus and occasionally even eating may fail to bring on the typical response. Psychic stimulation has not been observed to initiate the syndrome.

The patient was again seen at the Children's Medical Center at the age of 10 yr. Except for the auriculotemporal syndrome and numerous carious teeth, the routine physical and laboratory examinations were normal. On physical examination a scar 1.5 cm. long was present just above the angle of the left mandible and a similar scar just below the angle of the right mandible. A 2 cm. scar was noted 2 cm. below the angle of the left mandible. These scars were smooth, well healed, and without nodules, fistulae or tenderness. The skin of the cheeks was not abnormal to inspection; no abnormalities of touch, pain or temperature discrimination could be demonstrated. The pupils were round, regular and equal and responded well to light.

Twenty to 30 sec. of chewing an apple produced a mild flush of both cheeks, extending from

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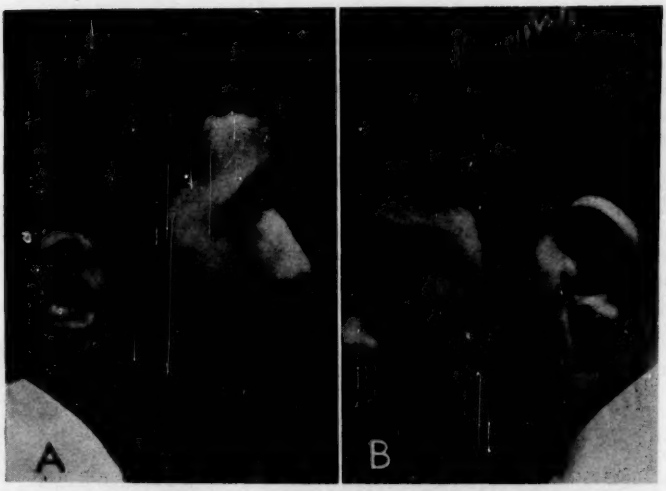

FIG. 1. Effect of chewing apple for 90 sec. Sweating demonstrated by starch and iodine application (Minor[39]). Approximate area of erythema indicated by dotted lines. A. Right. B. Left.

the tragus to the chin in a band 3 cm. wide parallel to the ramus of the jaw. After 60 sec. of chewing there was marked erythema of these areas, and pinpoint areas of sweat began to appear in the central portion. After 90 sec. of chewing, the reaction reached its height (figure 1). Further chewing did not produce any additional change; the area of redness was always larger than the sweating area. Within 60 sec. after chewing was discontinued, the erythema began to fade and within 5 min. was gone.

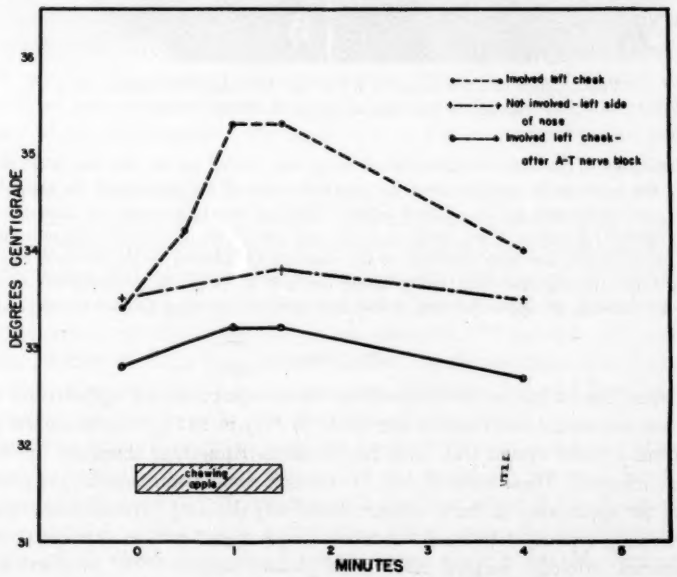

CHART 1. Changes in skin temperature produced by chewing apple for 90 sec.

The reaction could be provoked regularly by chewing and always reached its maximum intensity within 90 sec. A sponge soaked in 2% acetic acid held passively in the posterior right buccal cavity produced a delayed response: erythema began at 60 sec. and sweating did not appear until 3 min. afterward. At the end of 5 min., however, the erythema and sweating reached an extent and intensity similar to that seen after 90 sec. of chewing.

Chewing a dry gauze sponge produced a slight erythema in 30 sec. and slight sweating in 60 sec. Although the reaction started after a similar time interval, it never reached, even after 5 min., the intensity produced by chewing food.

The flushing of the cheeks was regularly accompanied by an increase in the skin temperature above that of the normal areas as is shown in chart 1; a rise of 1.9° C. was registered by a thermocouple on the surface of the erythematous area, while the temperature of the normal skin did not vary significantly.

Heat and pilocarpine sweating tests were not performed.

FIG. 2. Effect of chewing apple for 90 sec. Left auriculotemporal nerve blocked by procaine injection. A. Right. B. Left.

Anesthetization of the left auriculotemporal nerve was carried out by injecting 4 cc. of 1% procaine into the nerve as it emerges from the posterior edge of the condyle of the mandible. (This procedure was performed by Dr. Robert Smith, Chief of the Department of Anaesthesia of the Children's Medical Center.) A left facial paralysis and anesthesia of the left auriculotemporal area were produced. Nearly complete abolition of the response to chewing on the left side was produced for about 2 hr. although the facial palsy lasted but half an hour; no erythematous response was produced by chewing an apple and only a few tiny areas of sweating followed 5 min. of chewing (figure 2).

DISCUSSION

The earliest case of the auriculotemporal syndrome was presented by Baillarger in 1853,[2] but the first substantial contribution was made by Frey in 1923,[3] who described a case resulting from a bullet wound with secondary parotitis. Altogether about one hundred cases have been reported. These have all had in common some disturbance in the parotid area preceding the appearance of the syndrome. Externally draining parotitis, either primary[4-6] or complicating typhus,[7-9] typhoid,[4] abdominal operations[5, 11-14] or septicemia[5] has been the commonest etiology. Surgical removal of parotid tumors[4, 6, 11, 15] or direct trauma to the parotid area[16-18] have been reported as causes. Almost no adequately documented re-

ports have appeared in which the syndrome has followed disease of the parotid area in which there was no anatomic division of continuity of the tissues.

The cardinal signs of the auriculotemporal syndrome are precipitated by eating, and consist of flushing and sweating in the skin of the face supplied by the affected auriculotemporal nerve. Subjective complaints may or may not be present: feelings of warmth, although frequent, are seldom troublesome; pain, in some cases, may be severe. Perspiration varies from slight moisture to large quantities of fluid which may occasion considerable embarrassment at mealtime.

A latent period of several weeks to a few months usually separates the injury from the appearance of the syndrome although some well documented cases appear to have shown the reaction within a few days of the injury.[7, 18] Once the typical gustatory response is noted, neither progression nor improvement is to be expected; some patients have been followed as long as 40 years without change.[4, 6] As in the present case, the flushing component may precede the sweating by several months or even years.

In the majority of patients, acid or spicy food is a more potent stimulus than is bland food. Tasting without chewing is less likely to provoke the reaction, and the chewing of tasteless material in most patients is without effect. In general, any stimulus to salivation is sufficient to initiate the abnormal response; in some individuals psychic salivation is accompanied by malar flushing and sweating on the involved side.[6, 19] Erythema generally appears after one minute or less of chewing, and sweating follows shortly thereafter; the reaction continues unchanged for the duration of the chewing and fades away within a few minutes afterward.

Physical examination of the face usually shows some alteration of sensation in the skin supplied by the auriculotemporal nerve, commonly in the form of hypesthesia, although hyperesthesia may be found. That sympathetic control of the affected skin area is disturbed has been shown by the absence of sweating and temperature rise in the abnormal area in response to environmental heating.[4] Disturbance in the parotid gland may be associated, such as loss of gland substance, salivary fistula or lack of salivary secretion; facial paralysis, permanent or transient, may be produced by the original injury due to propinquity of the facial nerve to the involved area. These abnormalities are not causal, but coincidental.

Certain related phenomena have been reported which must share at least a partial etiologic similarity. Uprus et al.[27] presented a case of gustatory sweating involving a small submental area which followed removal of infected cervical lymph nodes, and presumably involved injury to the cutaneous colli nerve. Gustatory sweating of the entire half of the face has been reported in a number of diseases accompanied by dysfunction of the cervical sympathetic nervous system such as syringomyelia,[28, 29] cervical rib[30] and cervical sympathetic ablation.[4, 6] Since these are not mediated by the auriculotemporal nerve, they do not, strictly speaking, belong to the syndrome, although there is a basic resemblance and any etiologic hypotheses must take them into consideration.

The auriculotemporal nerve arises from the posterior division of the mandibular nerve and enters the parotid area between the ear and the condyle of the mandible. It courses beneath the parotid gland and anastomoses with the facial nerve before becoming superficial to provide the sensory supply to the skin of the temple, the anterior parts of the ear and part of the cheek. From the glossopharyngeal nerve it receives parasympathetic parotid secretory fibers by way of the otic ganglion. In addition it contains sympathetic sudomotor and vasomotor fibers derived from the cervical sympathetic ganglia via the

carotid plexus. The sweat glands of the face are innervated by the cervical sympathetic outflow, the postganglionic fibers of which are distributed with the peripheral branches of the trigeminal nerve. Sweating of the face in response to heat is mediated by the sympathetic pathways as has been regularly demonstrated by the absence of heat sweating in the face following cervical sympathetic ganglionectomy.[6, 31] These sympathetic nerve endings, contrary to the general rule, are cholinergic rather than adrenergic.

It has been repeatedly suggested, although never proved beyond question, that there also is a parasympathetic innervation of the sweat glands of the face. The best evidence available on this point was obtained by Wilson[31] in a patient with a cervical sympathectomy who was able to abolish gustatory sweating in the area supplied by one supraorbital nerve by local nerve block. List and Peet[6] draw similar conclusions from their studies on pilocarpine sweating in areas of sympathetic denervation.

In certain individuals there is a normal gustatory sudorific reflex, usually brought on by highly spiced or acid foods. Brown-Sequard himself[32] showed sweating of the upper lip in response to eating chocolate. Wende and Busch[33] have collected a number of such cases, most with marked familial association, who displayed gustatory sweating of the upper lip, nose and forehead brought on by eating specific foods. The relation of this unusual physiologic reflex to the auriculotemporal syndrome is hypothetic but suggestive; there must exist, in some individuals at least, a physiologically active mechanism which produces facial sweating in response to gustatory stimulation. Kaminsky[28] and Guttman[29] suggested that the auriculotemporal syndrome might be a release phenomenon in which this previously latent sweating mechanism is made manifest by damage to the sympathetic sudorific pathways in the auriculotemporal nerve.

Any etiologic theory must explain three confirmed observations: that the syndrome is mediated through the auriculotemporal nerve; that the cervical sympathetic system plays no active role in the syndrome; and that there is a local hypersensitivity of the sweat glands to acetylcholine. Anesthesia of the auriculotemporal nerve has repeatedly been shown to abolish the reflex, while cervical sympathetic block does not.[4] Freedberg et al.[4] found that less locally injected acetylcholine was required to produce sweating on the affected side than on the normal side. Any theory which also explains the gustatory sweating following cervical sympathetomy gains considerable force, for although there is no proof of a common mechanism, such would seem a logical assumption. In general, etiologic considerations have been of two main classes: one, that abnormal nervous impulses may produce the syndrome by acting on normal sweat glands; two, that normal nervous pathways are responsible by stimulating abnormally sensitive sweat glands. Perhaps both concepts are necessary to explain all cases of the phenomenon.

The former theory was early proposed by Trioumphoff[8] and supported by Needles[15] and Noica and Bagdasar[10] who suggested that swelling of the abnormal parotid gland accompanying salivation irritated the contiguous auriculotemporal nerve. This is unlikely in view of the persistence of the syndrome in unchanged form over periods of years during which parotid activity has returned entirely to normal or, in some cases, after the gland has presumably been completely destroyed or removed. A similar hypothesis was advanced by List and Peet[6] who thought scars and attempts at regeneration might result in abnormal irritability in the sudorific nerve fibers.

By analogy with cross innervations occurring following division of other peripheral nerves, Ford[34, 35] suggested that the auriculotemporal syndrome might be the result of misdirected regeneration of nerve fibers. Since each proximal neuron stump regenerates

by growing a "brush" of neurofibrils down the peripheral segment of several neurons, he reasoned that some salivary secretory fibers could grow down the course of sudorific fibers and innervate sweat glands after regeneration is completed. The latent period before development of the syndrome would coincide with the period during which regeneration is taking place. This hypothesis, however, fails to explain the cases without latent period or with a latent period of a few days, nor does it account for the development of local sensitivity of the sweat glands to acetylcholine. Gustatory sweating following cervical sympathectomy, of course, cannot be explained by this mechanism.

Hypersensitivity of effector structures following denervation is a commonly accepted physiologic principle, in both cholinergic and adrenergic nerves. Hypersensitization of the sweat glands of the face following division of the sympathetic supply in the auriculotemporal nerve is a logical expectation and is the second type of etiologic hypothesis.[4] This is proved by the demonstration by Freedberg et al.[4] and Langenskiöld[14] of increased sensitivity of the sweat glands in the auriculotemporal area to locally injected acetylcholine.

Hypersensitivity to acetylcholine appears to be an essential component of gustatory sweating. The source of acetylcholine in the area in question remains in doubt, but it must appear in response to nervous impulses over the peripheral branches of the trigeminal nerve. Several possibilities have been mentioned. The somewhat hypothetic parasympathetic sudorific nerve supply has been suggested by List and Peet[6] and by Freedberg et al.[4] as initiating the sweating response by way of some normally inapparent gustatory reflex; this type of reflex was originally proposed by Frey[3] who outlined a pathway from the nucleus salivatorius to the sweat glands through the otic ganglion. This may be identical with the reflex circuit which causes the occasional case of gustatory sweating in normal persons although Freedberg et al.[4] present some evidence that this latter reflex is in part dependent on the cervical sympathetic system, and that it may occur independently in a patient with the auriculotemporal syndrome. It may be that in some cases misdirected regenerating salivatory fibers, as suggested by Ford,[34, 35] are involved. The rapidity and uniformity of response make it unlikely that acetylcholine could diffuse into the area from neighboring nerve endings,[4, 6] although this has been proposed by Langenskiöld.[14] However, in this regard a case reported by Mellinkoff and Mellinkoff[36] is of interest. They describe an infant of 8 months who developed a sweating area, 6.3 cm. in diameter, over the left tibial tubercle every time she was given milk. The phenomenon was transitory, lasting only a few weeks, and coincided with a period of active crawling. The authors point out that there can hardly be any direct nervous connection which could mediate a gustatory response in the knee, and postulate a local irritation of the cutaneous sudorific nerves by crawling, which sensitized the sweat glands to circulating acetylcholine produced by vagal stimulation accompanying sucking. The points of similarity of this unusual case to the auriculotemporal syndrome are obvious, but the differences suggest that there may be more than one mechanism of stimulating the sensitized sweat glands.

The etiology of the auriculotemporal syndrome, it must be concluded, is not completely explained. Good evidence is available that there is a local sensitivity to acetylcholine in the area involved, and that the response can be blocked by section or anesthesia of the auriculotemporal nerve. Evidence available at present seems to indicate that the response is mediated either through normal nerve pathways which are not usually effective in the intact individual, or through abnormally regenerating fibers following injury.

Reports of the auriculotemporal syndrome in children are rare. Of 17 patients at the Children's Medical Center who had incision and drainage of parotid or cervical abscesses

or removal of parotid tumors, and were available for follow-up study, the present patient was the only one so affected. New and Bozer[18] reported a case following parotitis of the newborn infant which was accompanied by a permanent facial palsy with some elements of a mass facial nerve reflex. Uprus et al.[27] reported an analogous case in a 5 year old child who developed an area of gustatory sweating and flushing involving the right submental region following removal of infected cervical lymph nodes and presumed incidental injury to the cutaneous nerves of the region. The flushing component in this case preceded the sweating component by a two year period. McDwyer[37] and Barbosa[38] have reported two cases in nursing infants, the former without history of injury to the parotid area and the latter with a facial palsy presumably due to forceps injury of the parotid area; these cases resemble each other in that the gustatory response consisted of flushing without sweating in the auriculotemporal area. The experience in the case of Uprus and in the present case suggests that the infants, both being under 2 years of age, might have developed the sweating response later in childhood, but follow-up studies were not reported. It is interesting in this connection that in one of the families reported by Wende[33] the characteristic gustatory sweating response to certain foods appeared only at puberty.

Since the auriculotemporal syndrome is benign and nonprogressive, accurate diagnosis can be a source of considerable satisfaction to the patient. If the degree of discomfort or disability warrants, surgical section of the nerve can be performed with relief of symptoms. Alcohol injection as a method of treatment is to be avoided because of the possibility of injury to the adjacent facial nerve. In view of the efficacy of chemotherapy and x-ray in treating parotid abscesses, surgical intervention in this area should be avoided whenever possible.

Summary

The auriculotemporal syndrome is described. It consists of sweating and redness of the cheek brought on by eating in a person who has sustained injury to the auriculotemporal nerve in the region of the parotid gland. A case of the auriculotemporal syndrome is reported in a child following parotitis of the newborn infant treated by incision and drainage.

The basic etiology of the syndrome is unknown. Certain physiologic considerations are discussed. The condition is benign, nonprogressive and one in which surgical division of the auriculotemporal nerve should be curative. Surgical interference in the parotid area should be avoided whenever possible to prevent the possible occurrence of the auriculotemporal syndrome.

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SPANISH ABSTRACT

Sindrome Auriculo-Temporal; Reporte de un Caso y Revisión de la Literatura

El sindrome auriculo-temporal consiste en la occurrencia de perspiración y enrojecimiento de las mejillas provocados por el acto masticatorio en aquellas personas que han sufrido un traumatismo del nervio auriculo-temporal en la region de la glandula parotida. Se reporta un caso de sindrome auriculo-temporal observado en un niño siguiente a una parotitis ocurrida durante el periodo neo-natal la que fué tratada quirurgicamente (incisión y drenaje).

La causa basica de este sindrome es desconocida, pero los autores discuten ciertas consideraciones fisiologicas posibles. Esta condición es estacionaria y de caracter benigno, la cual puede curarse mediante la division quirurgica del nervio auriculo-temporal. Se recomienda evitar operaciones quirurgicas en el area de la glandula parotida con el objeto de prevenir la ocurrencia de este sindrome.

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GALACTOSEMIA IN INFANCY

Report of a Case with Observation for 24 Months

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GALACTOSEMIA is an uncommon disorder of carbohydrate metabolism characterized by the inability of the body to utilize ingested galactose. The symptoms and signs of this disease in infancy are: failure to gain weight, retardation of development, enlargement of the liver and spleen, melituria, excretion of albumin in the urine, often osteoporosis and cataract formation. Recognized instances of galactosemia are uncommon; only nine substantiated cases have been reported in medical literature.[1-11] A review of these cases emphasizes the importance of accurate diagnosis, since proper treatment, that is, elimination of galactose from the diet, results in clinical improvement, gain of weight, decrease in the size of the liver and spleen, and elimination of albumin and reducing substance from the urine. Evidence indicates that this clinical improvement is not associated with any alteration in the intolerance to ingested galactose, although follow-up studies over a long period have not been reported.

An infant with galactose intolerance has recently been observed for 24 months after the diagnosis was established.

REPORT OF CASE

A white male infant aged 4½ mo. was admitted to the hospital with the complaints of poor gain of weight, retarded development, pallor, vomiting and diarrhea since birth.

He was the fifth child of apparently healthy parents. The oldest sibling was 9½ yr. old and in good health; the second child had died at the age of 2½ mo. with symptoms of diarrhea and a diagnosis of cystic fibrosis of the pancreas; the third child had died at the age of 3 wk. of unknown causes; the fourth child was 2½ yr. of age and had nephrosis.

The patient was born at full term, after an uncomplicated pregnancy, but he failed to gain weight and was confined to the hospital for the 1st 3 mo. of life. He then was at home for 6 wk., but he did not gain, continued to vomit feedings and to have recurrent diarrhea.

Physical examination at the time of admission to the hospital revealed a pale, chronically ill, dehydrated baby whose weight was 4.3 kg., temperature 38.8° C. The eyes were sunken and the skin turgor was poor. The infant frequently emitted a shrill cry. The superficial veins of the chest and abdomen were prominent (fig. 1). The liver was felt 2.5 cm. below the costal margin. The neck and back were supple. The optic fundi on examination were not unusual.

Urinalysis revealed albuminuria, grade 2, and melituria, grade 2 to 3. RBC count 3.2 million/cmm; Hgb. 10.9 gm./100 cc.; WBC count 13.1 thousand/cmm. Sternal aspiration revealed normal bone marrow. Analysis of the duodenal contents showed normal amounts of trypsin and lipase but an absence of diastase. Tests for liver function revealed negative cephalin-cholesterol flocculation and normal thymol turbidity of 4 units. Blood urea measured 51 mg./100 cc. at the time of admission, but this later fell to 34 mg./100 cc. There were 5.3 gm. protein/100 cc. blood serum with 4.2 gm. albumin and 1.1 gm. globulin. Carbon dioxide combining power was 16.5 mEq./l. The results of examination of the cerebrospinal fluid were not unusual. Roentgenographic studies of the skull, chest and long bones failed to reveal any abnormalities.

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FIG. 1. Infant aged 4½ mo. Eyes are sunken, superficial veins prominent, abdomen distended.
FIG. 2. Infant aged 6 mo., following 6 wk. of galactose-free feedings.

The reducing substance was present in several specimens of urine. This was proved to be galactose rather than glucose by a series of tests. There was no fermentation by yeast. Mucic acid crystals were obtained which were identical with those of galactose. Phenylosazone crystals were identical in appearance and melting point with those prepared from a sample of pure galactose. Optical rotation was the same as that of galactose.

An oral galactose tolerance test was carried out with 7.7 gm. galactose (1.75 gm. galactose/kg. body weight, table 1). The value for blood sugar rose in 1 hr. from the fasting level of 113 mg./100 cc. to 295 mg./100 cc. It remained at 291 mg./100 cc. for 3 hr. and after 5 hr. it was still elevated at 210 mg./100 cc. Urine samples were collected while the test was carried out and all contained reducing substance in amounts graded 4 on the basis of 1 to 4.

An oral glucose tolerance test was done with 7.7 gm. glucose (1.75 gm. glucose/kg. body weight, table 2). A flat curve resulted with a fall in ½ hr. from a fasting level of 140 mg./100 cc. to 128 mg./100 cc. At 2 hr. the blood sugar measured 83 mg. and at 3 hr. 92 mg./100 cc. No reducing substances appeared in the urine during this test. The test was repeated and yielded a similar result.

Before the diagnosis of galactose intolerance was established by identification of galactose in the urine and the abnormal galactose tolerance curve, the infant continued to have fever, diarrhea and vomiting. He required parenterally administered fluids daily. However, he failed to gain weight in spite of transfusions of blood and an intake of foods that was calculated to contain adequate amounts of calories and vitamins. Finally milk was eliminated from the diet and a soy bean preparation was substituted. There was almost immediate clinical improvement, consisting of increased appetite, gain in weight and retention of fluid. The urine became free of reducing substance. Since

TABLE 1

GALACTOSE TOLERANCE TEST

(7.7 gm. galactose, 1.75 gm./kg.)

Time	Blood Sugar, mg./100 cc.	Urine Sugar
Fasting	113	No specimen
1 hr.	295	No specimen
2 hr.	291	Grade 4
3 hr.	291	No specimen
4 hr.	236	Grade 4
5 hr.	210	No specimen

the soy bean formula was not taken eagerly after the first week, nutramigen was used with excellent effect. The infant was dismissed to his home and gained 1.7 kg. in 5 wk. Re-examination at the end of this period of 5 wk. revealed general improvement in strength and color (fig. 2). The results of urinalysis were negative, and those of other laboratory tests were normal. The galactose and glucose tolerance tests were repeated, but the results were practically the same as those of the original tests.

At the age of 15 mo., 10 mo. after the milk had been eliminated from his diet, the baby was examined by his physician at home. He was able to stand but did not walk alone. His weight was 7.6 kg., which represented a gain of 3.3 kg. in 10 mo. The size of the liver had receded so that it was palpable only 1.5 cm. below the costal margin. The results of urinalysis were normal.

At the age of 24 mo. the boy was considered to be normal by his parents and his physician (Fig. 3). His weight was 8.4 kg. He walked and ran, his appetite was good and he ate almost all foods except milk.

COMMENT

This patient had the characteristic signs and symptoms of galactose intolerance. The expected favorable progress occurred when milk sugar was eliminated from his diet. Then he changed from a desperately ill infant to an essentially normal child by the time he was 2 years of age. The proper diagnosis was suspected because of the symptoms of failure to gain weight, large abdomen, diarrhea and vomiting, and the findings of an enlarged liver, melituria and albuminuria. The diagnosis was established by the identification of galactose in the urine. His inability to utilize galactose was further demonstrated by the abnormally high galactose tolerance curve. When galactose was eliminated from his food the galactosuria disappeared, as did the albuminuria.

This rare metabolic disorder must be differentiated from other diseases of infancy

TABLE 2

GLUCOSE TOLERANCE TEST

(7.7 gm. glucose, 1.75 gm./kg.)

Time	Blood Sugar, mg./100 cc.	Urine Sugar
Fasting	140	No specimen
½ hr.	128	Negative
2 hr.	83	No specimen
3 hr.	92	Negative
4 hr.	91	No specimen
5 hr.	83	No specimen

characterized by failure to gain weight, diarrhea and hepatomegaly. Glycogen storage disease involving the liver results in hepatomegaly due to excessive deposition of glycogen in the liver.[11] In this condition there exists a defect in glycogenolysis and a deficiency of glucose in the blood, together with retardation in growth, weakness, dyspnea, bleeding, susceptibility to infection, hepatomegaly and, occasionally, convulsions. Significant laboratory findings include fasting hypoglycemia, ketosis with acetonuria without glycosuria, and a minimal rise in blood sugar with the epinephrine tolerance test. The results of levulose and galactose tolerance tests are normal.

Hepatomegaly occurs in Gaucher's disease but the liver enlarges slowly and does not attain the size of the spleen, which assumes tremendously large proportions.[12] Cirrhosis

FIG. 3. Child aged 24 mo. Results of physical examination are normal, although wt. is only 8.4 kg. He runs and plays, eats all foods except milk.

of the liver produces hepatomegaly but is associated with jaundice and with evidence of disturbed liver function.[13] Leukemia and megaloblastic anemia usually can be differentiated by examination of the blood and bone marrow.

Pancreatic fibrosis and celiac disease must be excluded when dealing with an infant with symptoms of diarrhea and lack of gain of weight. In the former, trypsin is not present in the stools nor in the samples of duodenal secretions. In the latter the stools are bulky and foul smelling, the abdomen is enlarged but there is no deficiency of trypsin in the duodenal secretions and there is no melituria.

The pathogenesis of galactose intolerance is not known. Various hypotheses have been advanced by investigators who have had the opportunity to study infants with this rare disorder. One point of agreement is that the body mechanism for converting galactose into glycogen is not functioning properly, whether this takes place in the liver or in other organs or tissues. The cause of the symptoms of the disease has been postulated by Mason and Turner[4] as due to the secondary low blood glucose in addition to the toxic effect of

the elevated blood galactose levels. Bruck and Rapoport[7] contend that the low blood glucose level plays no part in the disease, because hyperinsulinism and glycogen storage disease do not cause the same symptoms and both conditions are associated with low blood glucose levels. That there may be a synergic relation between the mechanism for lowering the level of blood galactose and blood glucose is pointed out by Greenman and Rathbun[10] and illustrated by the accelerated lowering of the blood galactose level in their patient by giving glucose at the same time that galactose was administered. These authors emphasize the therapeutic implications of this observation: that a high glucose intake probably is desirable in the treatment of infants with galactose intolerance.

Although the number of reported cases of galactose intolerance is small, it is apparent that this is a specific disease with characteristic symptoms and signs which may prove fatal if not recognized. With elimination of galactose from the food, the symptoms subside promptly and the infant improves, although the fundamental intolerance for galactose may remain unaltered. A search of medical reports has failed to reveal any studies of the subsequent tolerance of galactose in these children; consequently, the ultimate prognosis in this respect has not been established.

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Spanish Abstract

Galactosemia en la Infancia; Reporte de un Caso Observado Durante Dos Años

La intolerancia a la galactosa es una condicion raramente observada en la infancia. Los sintomas caracteristicos de esta enfermedad incluyen: perdida de peso, emaciación, distención del abdomen con hepatomegalia y esplenomegalia, y ocasionalmente formación de cataratas. Galactosa y albumina están presentes en la orina. La elimimación de la galactosa de la dieta resulta en una mejoria del estado general del paciente y desaparición de la galactosuria y albuminuria.

Se describe un caso de galactosemia ocurrido en un niño de cuatro meses y medio de edad. La galactosa fué identificada en la orina cuando el niño ingeria leche, pero no se observaron substancias reductoras en la orina tan pronto la leche fué eliminada de la dieta. En los dos años de observación con regimen libre de leche, el paciente aparece sano y libre de melituria.

Mayo Clinic

AUREOMYCIN IN THE TREATMENT OF RUPTURED APPENDICES IN CHILDREN

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THE effects of aureomycin and streptomycin on experimental peritonitis in dogs have been studied by Yeager et al.[1] by creating a condition analogous to a ruptured appendix in the human. They obtained bacteria from the peritoneal exudate which were the same as those reported in human peritonitis from a ruptured appendix. With 10 dogs in each series, they reported a survival rate of 60% in 10 animals treated with streptomycin, 90% in 10 animals treated with aureomycin and 20% in the control series of 10 animals. The average mortality rate of clinical appendicitis with complications before the use of chemotherapy was 15%.[2-8] With chemotherapy, the mortality averages 6%. Crile[9] has reported a series of cases in which massive doses of penicillin were used with no mortality. The best therapy recommended for this condition is massive doses of penicillin combined with sulfonamide drugs used either separately or in combination. However, because of the toxicity, limited antibacterial activity, development of resistant organisms and a still significant mortality with use of these drugs, the study of another chemotherapeutic agent, aureomycin, was undertaken in the treatment of ruptured appendices.

Appendicitis may be caused by a variety of organisms growing in symbiosis. The most common bacteria found are Esch. coli, aerobic and anaerobic streptococci, clostridium, A. aerogenes and coliform bacilli and staphylococci. Since chemotherapy must be initiated before the results of cultures are known or when cultures cannot be obtained, the drug affecting the greatest variety of bacteria with the lowest toxicity would be the agent of choice. Aureomycin with its bacteriostatic effect on gram-negative and gram-positive organisms appears to fill these requirements better than previously available therapeutic agents.

Clinical cases of appendicitis are usually divided into three categories: (1) those with uncomplicated acute appendicitis; (2) those with appendicitis with rupture and localized abscess; (3) those with appendicitis with rupture and diffuse peritonitis. Only the last two classifications were included in this study as these make up over 90% of the mortality rate. The diagnosis was verified in all cases by surgery and culture.

It seemed advisable to report separately the pediatric cases because it is in this age group that the disease is the most difficult to diagnose and has the highest incidence of complications. The increased frequency of atypical cases and other simulating diseases, such as mesenteric adenitis, make the diagnosis more difficult for the pediatrician. Since he is frequently the first to see the patient, must make the initial diagnosis and is usually consulted for pre-operative medications, the medical aspects of the treatment are important to him. Appendicitis is most common in the second and third decades of life. It is rare before the age of 4 years but has been reported to have occurred as early as three

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days after birth. Because of the apparently infrequent occurrence in the younger age group, the proportionately abundant amount of lymphoid tissue in the appendix with the small lumen predisposes to severe inflammation, obstruction and perforation. A very small spread of the infection through the thin wall of the child's appendix brings it to the peritoneal cavity. The underdeveloped omentum in children does not wall off and localize the infection as the adult omentum does.

The following regime of dosage schedule has been established for the cases in this series: For patients under 5 years of age aureomycin* 500 mg. is given initially and then 250 mg. every 4 hours until clinical response is obtained. This dosage is changed to every 6 hours until the temperature is normal or the patient appears clinically well for 4 or 5 days. In older children the above schedule is probably adequate but it is safer to give 1 gm. initially and then 250 mg. every 4 or 6 hours. This dosage is probably more than adequate. At no time was it necessary to give the drug parenterally. If Wangensteen suction was being used, the aureomycin was given through the tube and then the suction was stopped for one hour. On a few occasions the initial dose was given by a retention enema in mineral oil. In small children the capsules were opened and the contents given in syrup.

The side effects of aureomycin have been minimal. The most troublesome problems were nausea, vomiting and anorexia. Changing the dosage to a six hour schedule or giving the drug in syrup[10] was most helpful in alleviating the nausea. Aureomycin was given rectally to one patient for 48 hours and then the drug was retained orally. At no time was it necessary to discontinue medication. Repeated checks on the blood and urine revealed no toxicity.

The same general management of these cases was carried out jointly by the pediatric and surgical departments. All patients were started on aureomycin when they returned from surgery. No chemotherapy was given. In all but a few of the older children, Wangensteen suction was instituted and continued until peristalsis was established, when oral feedings were started. All patients received parenteral fluids calculated to provide adequate water and salt, protein 3 gm./kg., vitamins and carbohydrate sufficient to make up at least maintenance calories. Blood and plasma were given only when necessary. Parenteral fluids were discontinued as soon as oral feedings were tolerated. Blood electrolytes; CO_2, Cl, Na, K and blood urea were followed and maintained by appropriate fluids. Oral feedings were first liquid, then a soft diet and later a regular diet was tolerated. The patients were encouraged to early oral feeding and early ambulation.

The abdominal cavity of each patient was cultured for bacteria at operation. The usual variety of organisms were cultured from the ruptured appendix (table 1). No correlation could be made between the rapidity of response and type of bacteria cultured.

The results on 16 children between the ages of 17 months and 12 years are shown in table 1. There were no fatalities. All but four of the cases showed favorable response in 24 to 48 hours as shown by temperature and clinical improvement. These four cases had a temperature fall by lysis and a more gradual response. A large abscess had formed about the appendix in these cases. Four of the 16 patients underwent no immediate surgery. In each case an operation was performed within three months of the acute phase of the illness and a fibrosed appendix or abscess-sac removed. One patient, because of the generalized peritonitis with abscess formation, had incision and drainage of the abscess

* Supplied through the courtesy of the Lederle Laboratories Division, American Cyanamid Co.

TABLE 1

CASES TREATED WITH AUREOMYCIN

Case	Age	Culture	Clin. Response	Aureo.	Surgery	Diagnosis with Appendicitis	Result
J.G.	6 yr.	None	24 hr.	10 days	None	Abscess Pneumonia	Good. 3 mo. later appendix removed.
W.T.	4 yr.	None	36 hr.	9 days	None	Abscess in L.L.Q.	Good. 6 wk. later appendix removed.
R.M.	12 yr.	None	Lysis	14 days	None	Abscess	Good. 3 mo. later appendix removed.
Z.W.	10 yr.	None	Lysis	8 days	None	Abscess	Good. 3 mo. later appendix removed.
C.M.	7 yr.	Esch. coli Staph. albus Clos. welchii	24 hr.	7 days	Appendectomy Drainage	Gen. peritonitis	Good
S.P.	10 yr.	Esch. coli	24 hr.	6 days	Appendectomy	Peritonitis	Good
R.L.	11 yr.	Esch. coli Clos. welchii	24 hr.	7 days	Appendectomy Drainage	Loc. peritonitis	Good
J.O.	20 mo.	No growth	36 hr.	12 days	Appendectomy Drainage	Gen. peritonitis Febrile convulsion	Good
J.M.	8 yr.	Str. viridans Esch. coli	30 hr.	9 days	Appendectomy Drainage	Peritonitis Tonsillitis	Good
C.B.	30 mo.	Esch. coli B. alcaligens	Lysis 72 hr.	9 days	Appendectomy	Gen. peritonitis	Good
B.G.	17 mo.	Esch. coli Str. viridans	48 hr.	8 days	Incision Drainage	Gen. peritonitis Abscess	Good. 3 mo. later appendix removed.
M.M.	10 yr.	Esch. coli Gamma strep.	48 hr.	13 days	Appendectomy Drainage	Gen. peritonitis	Good
G.B.	10 yr.	Str. viridans	18 hr.	5 days	Appendectomy	Gen. peritonitis	Good
W.H.	3 yr.	Esch. coli Ps. pyocyanea Gamma strep.	72 hr. Lysis	5 days	Appendectomy Drainage	Loc. peritonitis Abscess Pneumonia (PO)	Good
J.R.	30 mo.	Esch. coli Ps. pyocyanea Str. beta hem.	24 hr.	6 days	Appendectomy Drainage	Abscess	Good
D.H.	7 yr.	Staph. albus hem. Gamma strept.	36 hr.	4 days	Appendectomy	Gen. peritonitis	Good

as her immediate surgery and three months later a fibrosed appendix was removed.

The four cases in which surgery had to be postponed are of special interest. One was diagnosed on admission as questionable peritonitis because all the signs were in the left lower abdomen quadrant. He had been placed on aureomycin prophylactically and was beginning to improve by the time an abscess was palpable. Two patients had both been ill some time before admission and had large walled-off abscesses. Each showed a good clinical response and the size of the abscess gradually diminished. When these patients returned for appendectomy, the inflammation had subsided and adhesions were the only complications. The fourth case is reported in detail below.

In this series 5 of the 16 patients were under 4 years of age. This is explained by the increased incidence of complications; the infection was more severe and diagnosis more difficult in the lower age group. One patient was treated for a convulsion, another had unexplained fever, a third remained in the hospital 48 hours before any signs of pathology in the abdomen were found and the fourth was treated first for tonsillitis. All the patients in this group demonstrated a most gratifying recovery with aureomycin.

Case Reports

Case 1: A 6 yr. old female was admitted with a chief complaint of stomach pains. Five days prior to admission she had a cold and cough and for 2 days had been feverish and anorexic. Thirty-six hours before admission she began to vomit. The next day a diagnosis of pneumonia was made for which she was given an injection of penicillin and cough medicine orally. On admission she was toxic, febrile, vomiting, coughing and having severe abdominal right chest pain.

Physical examination: Temperature 39.4° C., pulse rate 120/mm., respiration 30, blood pressure 118/72 mm.Hg. She was lethargic and complained constantly of chest and abdominal pain on the

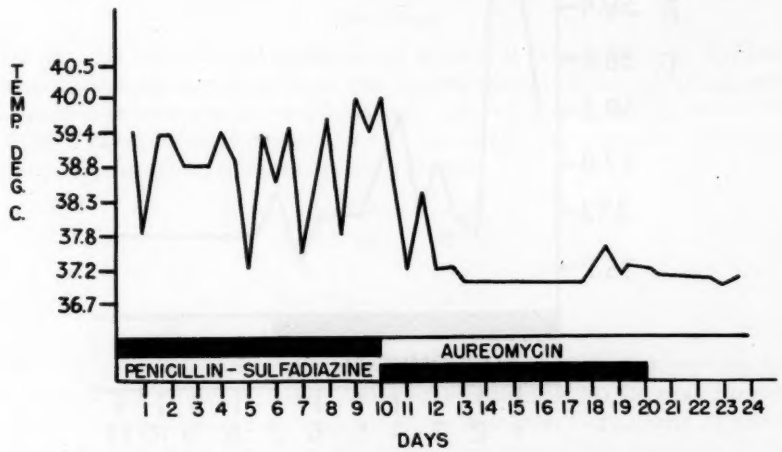

Chart 1. (Patient J. G.) Appendicitis with abscess and pneumonia. No operation.

right side. Throat was diffusely inflamed with a foul breath. Shotty cervical nodes were palpable. There was limitation of motion, dullness to percussion, breath sounds diminished both anteriorly and posteriorly. Spoken and whispered sounds were diminished over R lower chest. Abdomen was tender throughout but the most tender areas were in the right costovertebral angle, just below the liver margin in the anterior axillary line and over McBurney's point. There was muscle spasm over these areas.

WBC count was 19 thousand/cmm., Hgb. 14 gm./100 cc. Urine had 5 to 8 WBC/hpf and 20 RBC. Roentgenograms of chest revealed perihilar pneumonitis on right with extension to R cardiophrenic angle.

Because of hematuria, pneumonia and diffuse abdominal signs, immediate surgery was withheld and the patient was treated with fluids 1,200 cc./day, aqueous penicillin 30,000 u. every 4 hr. and sulfadiazine initial dose 2 gm. and then 1 gm. every 8 hr.

For the next 9 days there was no improvement. Temperature course is shown in chart 1. She received parenteral fluids early and then adequate fluids by mouth. Urine cleared of RBC, WBC, albumin and was negative on culture. On the morning after admission the blood urea was 7 mg./100 cc. and the sulfadiazine level was 5.3 mg./100 cc. WBC count was as high as 32.2 thousand/cmm. but the polymorphonuclear count never went above 53%. Pain was still present in R side and clini-

cally and roentgenologically the pneumonia had extended in R base and there was elevation of the R diaphragm. Four days after admission, a mass had developed approximately 7.6 cm. in diameter in the flank between the costal margin and the iliac crest.

Nine days after admission the mass was more definitely palpable. Pneumonia was still present. Temperature was still elevated and WBC count was falling with a reduction in the polymorphonuclear cells. Other chemotherapeutic agents were discontinued and aureomycin was begun, 250 mg. every 4 hr. orally. There was a rapid fall in temperature over 26 hr. and clinical improvement. Four days later aureomycin was changed to 250 mg. every 6 hr. and after 2 days chest was clear and the

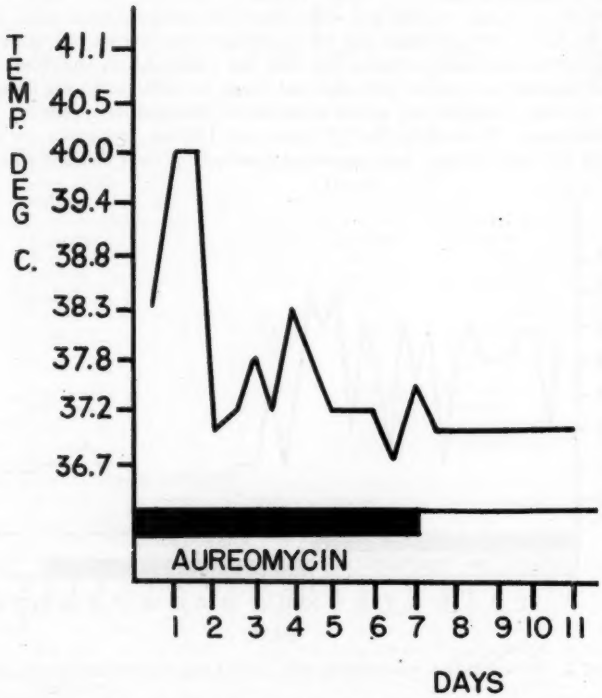

CHART 2. (Patient J. R.) Appendicitis with abscess and appendectomy.

mass disappearing. Twelve days after aureomycin was administered, the drug was discontinued as the patient was feeling well and was up and about. Eight days later she was ready for discharge.

Three months later the patient returned for an appendectomy at which the cecum was found in the RUQ surrounded by a healed abscess containing a fecalith. All that could be found of the appendix was a small 0.5 to 1.0 cm. stump. The abscess surrounded the right ureter and the entire area contained many adhesions. There were no complications after the operation and the patient was discharged on the 12th hospital day. Three months after the appendectomy the child was admitted to the hospital with volvulus secondary to adhesions. An exploratory laparotomy was performed and the adhesions separated. The patient did well and was discharged 9 days later. Since then she has had no further trouble.

Case 2: A 2½ yr. old male was admitted because of abdominal pain and vomiting. Present illness began 5 days before admission when he became restless and vomited. He was given an enema and paregoric but continued to vomit for 2 days. Tonsillitis was diagnosed. He appeared to improve but again vomited 24 hr. before admission. He refused to walk, frequently flexed his legs toward his

abdomen and cried as if in pain. Two enemas were ineffectual. During the 24 hr. before admission there was complete loss of appetite.

Physical examination: Temperature 38.6° C., pulse 120 mm., respiration 14. The patient was rather pale and appeared acutely ill. He kept his legs flexed. Abdomen was distended and no peristalsis was heard. Right rectus muscle was tense. Marked tenderness was present with dullness to percussion in R lower side. Rebound tenderness was present over R side. A mass could not be felt. On rectal examination R side was tender and thickened. Hgb. was 9.6 gm./100 cc. and WBC count 14.9 thousand cmm. Patient was taken immediately to operating room and an appendectomy was performed. Through a McBurney incision free, foul-smelling pus was found in the abdominal cavity; the appendix was located and removed. A perforation was present in the middle of the appendix. A Penrose drain was inserted and the abdomen closed.

Postoperatively the patient was given aureomycin 1 gm. orally which he immediately vomited. The dose was repeated in 1 oz. of mineral oil by rectum which was retained. The patient was then started on 250 mg. every 4 hr. dissolved in syrup, orally. By the next day the temperature was falling (chart 2) and the patient much improved. Peritoneal culture taken at operation showed Esch. coli, Str. beta hemolyticus and Ps. pyocyanea. Patient was discharged completely well 100 days later.

Discussion

The fact that there were no deaths in this series is of limited statistical significance because of the small number of cases. The reported mortality figures for all ages when other antibiotics were used for complications of ruptured appendices range from 4.9%[2] to 13.9%.[4] Ladd's mortality figures[11] for his series of ruptured appendices with local or diffuse peritonitis without chemotherapy are as follows:

Under 1 yr.	50%
1 to 2 yr.	22.7%
2 to 4 yr.	11.7%
4 to 6 yr.	5.2%
6 to 12 yr.	3.2%

These figures are comparable with the series reported here as they represent the same age group. While the present authors' series was accumulating, Wright et al.[12] reported 52 cases of peritonitis treated with aureomycin. In their series they reported 35 cases of peritonitis from ruptured appendices with two deaths (seven of these cases, but none of the deaths, were in children). One of the deaths was due to a pulmonary embolism and the other due to the postoperative rupture of an appendiceal stump. In 145 cases of acute peritonitis of appendiceal origin receiving the same treatment except different antibiotics, they report a mortality of 10.3%. Yeager,[13] in reporting the total series at the University of Maryland Hospital, has had no deaths in 39 cases. While it is too early to draw definite conclusions regarding the efficacy of aureomycin, it appears that aureomycin is probably superior to previously used antibiotics in the treatment of ruptured appendix.

Summary

A report is given on the use of aureomycin as the sole antibiotic therapeutic agent in 16 cases of peritonitis or abscess complicating appendicitis occurring in children. In four of the cases surgery was postponed because of the child's condition. There were no deaths in this series.

Aureomycin appears to be the drug of choice when combined with surgery in treating appendicitis with abscess or peritonitis or to be used alone when surgery must be postponed. A satisfactory dosage schedule for aureomycin is given.

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SPANISH ABSTRACT

Tratamiento con Aureomicina de las Perforaciones Apendiculares en Niños

Se describen los resultados del tratamiento con aureomicina como unico antibiotico, en 16 casos de apendicitis complicada con peritonitis o abscesos apendiculares en niños. En cuatro de estos casos el tratamiento quirurgico tuvo que ser deferido debido a la condicion del paciente. No se registraron defunciones en esta serie.

La aureomicina parece ser la droga indicada en el tratamiento de las apendicitis complicada con abscesos o con peritonitis, ya bien sea combinada con el tratamiento quirurgico, o sola, cuando la cirujia tiene que deferirse. Los autores indican la dosis satisfactorias de aureomicina para estas condiciones.

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NEPHROTIC SYNDROME IN RATS

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THE chronic renal disease in rats induced by the intravenous injection of anti-kidney serum obtained from rabbits, as it was first studied by Smadel and Farr,[1,2] simulates in many ways the nephrotic syndrome as seen in infants and children. This is especially true in the Long-Evans strain of rats, the clinical and pathologic aspects of which are herein reported.

METHODS

Antisera against rat kidneys were prepared by injecting rabbits with suspensions of perfused rat kidneys. The procedure described by Smadel[1] was first used, but underwent modifications later on. For perfusing the kidneys, 0.9% NaCl solution was run into the thoracic aorta at a hydrostatic pressure of 1 meter, until the kidneys were grossly free of blood. When the perfusion failed, the animals were discarded. The kidneys were removed, weighed, and 0.9% NaCl solution was added to make a 50% suspension. A fine suspension was obtained by placing the material in a Waring Blendor for 5 min. After adding toluene and penicillin 1,000 u./cc. the suspension was placed in an incubator at 37° C. for 24 hr. The material was cultured and those preparations giving any bacterial growth were not used. The suspensions were stored frozen indefinitely.

Rabbits weighing about 2500 gm. were injected intraperitoneally with 10 cc. of a 10%, 15% and 20% suspension every other day for the 1st wk. Twenty per cent suspensions were used for the 2nd and 3rd wk. Six days after the last injection 20 to 30 cc. of blood was obtained by cardiac puncture. This treatment was repeated after 2 wk. rest 3 to 5 times in the same rabbit. This procedure was found to yield highly nephrotoxic sera almost regularly. Trials to improve the yield of active sera by using Freund's[3] adjuvant technic were disappointing.

The rabbit serum was heated at 56° for half an hour to diminish its primary toxicity. It was stored frozen until used. It was noted repeatedly that the nephrotoxicity of the sera increased after they had been stored frozen for many months. Intradermal tests performed with rat kidney suspensions in the treated rabbits bore no relation to the nephrotoxicity of their sera. Antibody titrations were not undertaken, as Smadel[1] has shown that the nephrotoxic activity of anti-kidney serum cannot be correlated with its precipitin titer for kidney extracts. Biologic assay remains thus far the only means of determining the amount of nephrotoxin in an antiserum.

It has been shown[4] that after intravenous injection renal antibodies are selectively absorbed in the kidneys. It thus seemed advisable to gauge the amount of nephrotoxic serum to be injected into a rat according to kidney weight rather than body weight. A series of kidney weights of healthy rats weighing 30 to 500 gm. was obtained and plotted. The weight of both kidneys thus could be estimated in any rat to be injected. 1.4 cc. of serum (R-dose) fractions (R/2 to R/24) or multiples (2 to 3 x R) thereof, depending on the nephrotoxic activity of the serum, per 1 gm. renal tissue were injected (table 1). One third of the dose was given by intravenous injection on each of 3 consecutive days.

Rats of the Long-Evans strain were used exclusively. They were fed Friskies and had unrestricted access to water. They were weaned when 3 wk. old, received Friskies for 1 wk. and were injected usually at the age of 4 wk., weighing approximately 50 gm. Occasionally, however, an older animal, weighing 100 to 150 gm. was chosen. All rats were kept in separate cages. Urine was obtained once

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TABLE 1

AMOUNT OF NEPHROTOXIC SERUM INJECTED INTO RATS, GAUGED ACCORDING TO KIDNEY WEIGHT

Wt. of rat (gm.)	Wt. of kidneys (gm.)	Amount of serum (cc.) (R)
40	0.45	0.63
50	0.55	0.77
60	0.65	0.9
70	0.75	1.0
100	1.0	1.4
150	1.30	1.8
200	1.55	2.1
250	1.75	2.4
300	1.95	2.7
350	2.15	3.0
400	2.3	3.2

or twice weekly in all animals. They were placed over-night in metabolism cages without food and water. The receptacle was covered with a rubber ring to prevent evaporation, and contained 2 drops of a 6% formalin solution. The reaction of the urine specimen was almost always acid to litmus when tested the next morning. The urine was tested for albumin by boiling, and 1 to 2 drops of a 3% acetic acid solution was added. Table 2 shows the relation of these tests to quantitative protein determinations. The centrifuged sediment of every urine showing more than a 1+ albumin reaction was examined microscopically. The specific gravity was measured in freshly voided specimens with the falling drop method after water had been withheld for 4 hr. in some rats, while in others this precaution had not been taken. The blood pressure of the rats was taken with the foot method described by Kersten, Brosene, Ablondi and Subbarow.[5] In the evaluation of the readings the age conditioned differences in the blood pressure of rats[6] were taken into account. The following values

TABLE 2

RELATION OF QUALITATIVE ALBUMIN REACTION TO QUANTITATIVE PROTEIN DETERMINATIONS IN URINE OF RATS

Intensity of qualitative reaction	Protein gm./100 cc.	Protein gm./24 hr.
0	0.35–0.45	0.006–0.015
SPT	0.3 –0.8	0.012–0.017
+	0.5 –1.3	0.008–0.036
++	1.0 –3.0	0.02 –0.15
+++	2.5 –5	0.08 –0.3
++++	3.0 –6.0	0.3 –0.6

for the systolic blood pressure were considered normal: for rats weighing 50 to 100 gm. not more than 90 mm.Hg; for rats weighing 100 to 350 gm., 120 mm.Hg and for rats weighing more than 350 gm., 140 mm.Hg.

RESULTS

The following discussion is based on the observation of 235 rats of the Long-Evans strain in whom renal disease had been produced. Autopsies were performed on 183 animals and histologic studies of kidney, liver, lung, pancreas and aorta were obtained in 157. Seventy-eight different nephrotoxic sera were used which had been obtained from 33 rabbits.

Whenever adequate amounts of a nephrotoxic serum were used, proteinuria was ob-

TABLE 3

SPECIFIC GRAVITY OF URINE OF CONTROL AND NEPHROTIC RATS THAT HAD UNINTERRUPTED ACCESS TO WATER

Duration of disease (mo.)	Severity of disease	Specific gravity*	Controls' specific gravity
½	++	1.0415	1.0217
1	+++	1.0341	1.0347
1	+++	1.0449	1.0386
1	+++	1.0504	1.0396
		1.0392	1.0411
		1.0428	1.0411
1¼	+++	1.0614	1.0421
		1.0121	1.0317
1½	+++	1.0250	1.0148
1¾	++	1.0266	1.0156
2	++++	1.0571	1.0215
2	++++	1.0508	1.0220
3	+++	1.0622	1.0462
		1.0250	1.0505
4	+++	1.0248	1.0555
4	+++	1.0549	1.0562
		1.0435	1.0567
4	+++	1.0257	1.0164
		1.0397	1.0481
		1.0404	1.0568
4	+++	1.0454	1.0583
		1.0507	1.0646
6	+++	1.0614	
7	++++	1.0458	
7	+++	1.0374	
		1.0497	
8	+++	1.0530	
		1.0269	
		1.0533	
9	++++	1.0514	
10	+++	1.0500	
		1.0540	
		1.0543	
		1.0030	
	AVERAGE:	1.0434	1.0399

* Corrected for urinary proteins.

served without delay. The urine usually showed a 3 to 4+ albumin reaction within 24 hours after the last injection of serum. Gross hematuria was not observed and positive benzidine reactions were obtained in the sediment at onset in 64 (27.2%) rats. Within 1 to 2 weeks, this initial microscopic hematuria subsided. An occasional positive benzidine reaction in later stages of the disease was observed in 15 (6.3%) rats. A continuous hematuria, present more or less uninterruptedly during the entire course of the disease, was never noted. Hyaline and granular casts were often seen after the disease had been established for a few days. White blood cells in large amounts or in clumps were rarely noted. The specific gravity was measured in 111 urine specimens of 41 sick rats that had

uninterrupted access to water. Some of the values obtained in different stages of the disease are shown in table 3. They do not differ from those obtained in 22 healthy animals. If water was withheld for four hours, the urine of 20 healthy rats had a specific gravity that varied between 1.037 and 1.069. Among 19 nephrotic animals similarly treated, the values were, however, consistently lower than the lowest values obtained in control animals in five rats. An inability to concentrate thus became manifest in 26%.

Ascites and edema (Figs. 1, 2 and 3), usually localized in the region of the neck and less frequently in the lower extremities, was observed in 84 (35.7%) rats. Anasarca developed usually 3 to 4 days to 2 weeks after the disease had been induced and lasted 1 to

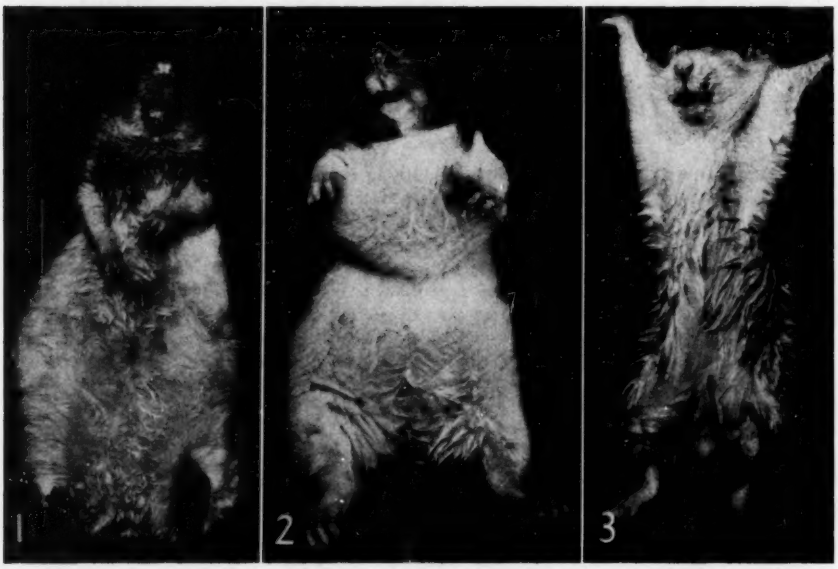

FIG. 1. Rat #197 18 days after injection of Serum 471C. Doses: R/2. Marked degree of ascites without edema.

FIG. 2. Rat #97 W 4 days after injection of Serum 488C. Doses: R/2. Marked degree of edema of face, neck, chest, lower extremities; also ascites.

FIG. 3. Rat #209 11 days after injection of Serum 474C. Note edema of lower extremities and scrotum.

3 weeks. Ascites and edema in late stages of the disease were seen only once. It was noted in this animal after proteinuria had persisted for 8 months and lasted 4 weeks. The amount of ascitic fluid varied between 5 and 9 cc. Fluid in the pleural cavity (4 to 6 cc.) was observed in 40 rats. Subcutaneous edema could occasionally be aspirated and 2 to 3 cc. of fluid were obtained. The fluid was slightly milky and turbid. Scrotal edema was noted in five animals.

The duration of the disease varied greatly. Seventy-seven rats (32.8%) died within the first two weeks. Most of these had ascites, edema and massive proteinuria and frequently developed diarrhea. Convulsions were never observed. A spontaneous cure of the disease was observed in 70 animals (29.8%). In 73% of these the proteinuria subsided within 4 weeks. In 19% the spontaneous cure occurred during the second month. A

TABLE 4

RESULTS OF BLOOD CHEMISTRY STUDIES IN DIFFERENT STAGES OF NEPHROTIC RATS AND IN CONTROL ANIMALS

Duration of illness (mo.)	NPN mg./100 cc.	Average	BUN mg./100 cc.	Average	Creatinine mg./100 cc.	Average	Serum Protein gm./100 cc.	Average	Cholesterol mg./100 cc.	Average	Total Lipids mg./100 cc.	Average	Lecithin mg./100 cc.	Average
½–1	38-43-44-56- 56-62-65-70 70-73-78-79 90-98-100 123-133-135 177-187-193 225-235-268	112	42-70-80 172-204-240 330	164	0.7–0.8–1.0 1.1–1.2–1.3 1.4–1.4–1.5 1.7–1.7–1.7 2.3–2.7–3.4	1.6	1.7–1.7–1.5 1.8–1.8–1.9 2.1–2.2–2.3 2.4–2.4–2.6 2.9–2.9–2.9 2.9–3.4–3.8 3.9–4.0–4.1 4.3–4.3–4.5 4.7–4.8–5.6 5.7–6.3–6.6	3.44	60–110-160 160-188-220 290-290-310 315-425-430 465-490-445 500-535-590 670-1960	430	380-440-910 910-1240 1520-1620 1990-2200 2470-3030 3610-6490 19500	3300	645	
1–2	34-45-49-50	44.5	62		1.2–1.5–1.9 2.6	1.8	3.3–3.9–5.4 6.3	4.7	135-270-445 480-535	372	1700-1820 2930-3360	2450		
2–6	55-58-60-69	60.5	25-27-42	31.2	1.2–1.4 1.6–1.9–5.0	2.2	3.6–3.7–4.3 5.0–5.2	4.4	90-110-125 215-310	170	210-620-720 880-1800	845	222	
6–13	39-40-45-44 47-50-52-53 95-162	62.7	17-18-23 25-49-80 90	43	0.9–1.2–1.2 1.3–1.3–1.5 1.5–1.6–1.7 1.8–2.3	1.5	2.6–4.4–4.4 4.6–4.7–4.8 4.6–5.0–5.0 5.8–5.9	4.8	65-65-70-80 85-95-100 130-135-165 245-555	149	230-240-300 310-500-500 760-1060 4120	866	136-162-166 190-185-200 258-398-725	269
Controls		45		25		1.33		6.5		90		400		170

negative albumin reaction in the urine was obtained in the remaining six rats, 5 to 8 months after the disease had been induced. An uninterrupted, chronic renal disease was observed in 32 (13.6%) rats for as long as 13 months. In 13 additional animals (5.5%) the course was characterized by spontaneous remissions and exacerbations. Aside from the 77 rats that died, from a fulminating renal disease within the first two weeks, not one of the chronically ill rats died spontaneously of the renal disease. Fifteen animals were, however, killed for various reasons after 7 to 14 months. A moderate anemia (Hgb.$<$14 gm./100 cc., RBC$<$8 million/cmm.) was noted in three of these rats, 9, 10 and 11 months after onset. Intercurrent infections were conspicuously rare. Only three rats died of pneumonia.

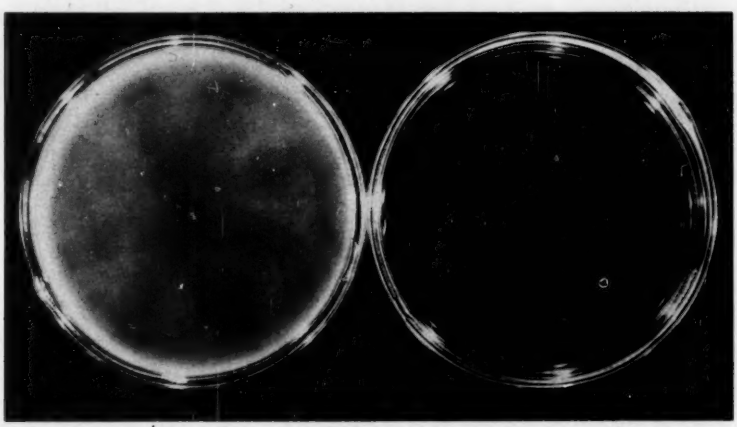

FIG. 4. Milky serum of Rat #90 (left) compared with serum of control rat (right). This serum was obtained 2 wk. after injection of Serum 476. NPN 56 mg./100 cc., cholesterol 500 mg./100 cc., total lipids 3610 mg./100 cc.

The blood pressure was taken every 1 to 2 weeks in 125 sick rats. Ninety-two animals (74%) remained at all times normotensive. In 60 of these (48%) the disease was of short duration, lasting not more than two months. Among the remaining 32 (26%), the duration was from 2 to 7 months in 17, and from 7 to 14 months in 15. Some hypertension was noted in 33 (26.4%) rats. Only three of these (2.4%) showed a continuous elevation of the pressure, whereas fluctuating hypertensive values were observed in seven (5.6%) chronically ill animals. In three further rats (2.4%) the elevation of blood pressure was only noted in late stages of the disease, whereas the remaining 20 (16%) animals had high values (often only one or two successive readings) within the first two weeks of their disease.

The results of blood chemistry studies in different stages of the disease are summarized in table 4. In the acute phase, hypoproteinemia was marked and improved gradually as the disease progressed. Normal values were, however, not obtained even in late stages. Hyperlipemia involving cholesterol, lecithin and total lipids was also most marked at onset and gradually decreased later on. The values remained elevated, however, as long as the disease lasted. It was observed regularly and often was so intensive that the serum looked like milk (Fig. 4). Marked azotemia was almost regularly found at onset of a severe

disease. It was usually not associated with increased creatinine values in the blood, hypertension, or hyposthenuria. The NPN and BUN values decreased after the first 3 to 4 weeks to normal, and remained normal in 50% of the rats even when the renal lesion had lasted for 6 to 13 months. In the remaining animals (50%) slight to moderate degrees of azotemia were noted in late stages of the disease. The kidneys of sick rats were large (Fig. 5), pale, and of a yellow-grayish color. The capsule was on occasion adherent. The surface was smooth, with the exception of 28 (15%) in whom the surface was coarsely granular. In eight (4.4%) rats that died within the first two weeks pinpoint-sized, reddish, bluish spots were noted on the surface.

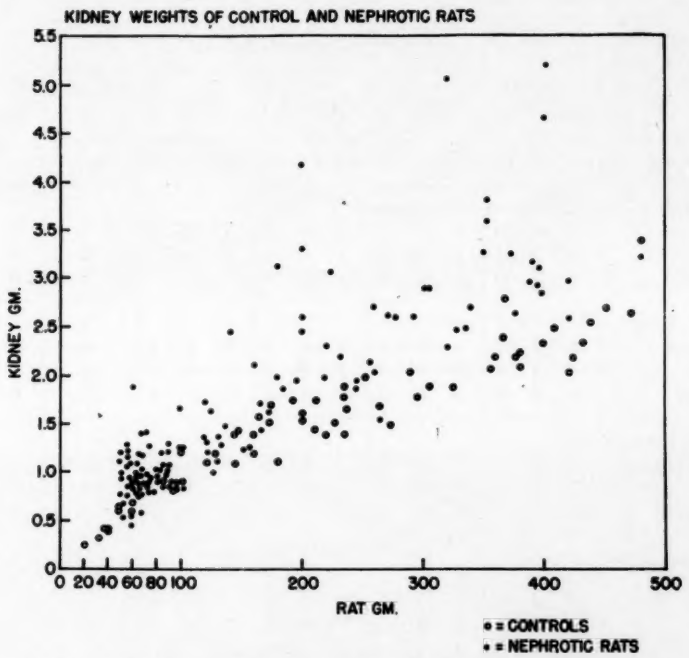

FIG. 5. Illustration of increased weights of kidneys of nephrotic rats.

An analysis of the histologic changes observed in 119 sick,* 12 recovered and 31 control rats is summarized in table 5. The findings are grouped according to severity of the histologic lesion and in relation to the duration and severity of the disease. This was classified as mild when a 2 to 3+ albuminuria was the only manifestation that subsided within 4 to 12 weeks. It was classified as moderately severe when a 3 to 4+ albuminuria was not associated with edema and ascites and did not subside within the first two months. A severe disease was assumed when a 4+ albuminuria was associated with edema and ascites soon after onset. The severity was classified as fulminating when a 4+ albuminuria, massive edema and ascites developed and when the animal died within the

* The findings obtained in 38 additional cases were omitted from this discussion as they showed some autolysis or because the administration of certain agents might have altered the findings.

first three weeks. The controls were largely untreated animals. A few of them received injections of innocuous sera and never showed clinical evidence of a renal disease. They are grouped according to age permitting comparison with sick rats of similar age groups.

Diffuse and Focal Glomerular Lesions (Figs. 6, 7, 8 and 9): In the early stages of severe and fulminating disease definite diffuse glomerular lesions were demonstrable in 72% of the animals. Slight and focal lesions were found in some of the remainder. In moderately severe disease, definite lesions were demonstrated in about 11% and slight

TABLE 5

HISTOLOGIC CHANGES IN 119 SICK, 12 RECOVERED AND 31 CONTROL RATS

	Controls			Diseased Animals										Recovered		
				Mild			Moderate			Severe			Fulminating			
Duration (mo.)	0–1	2–5	6+	0–1	2–5	6+	0–1	2–5	6+	0–1	2–5	6+	0–1	0–1	2–5	6+
Fatty Degeneration of Tubules and/or Glomeruli*																
Negative	12	11	3	6	12	0	4	0	0	1	1	1	9	0	2	3
Slight	0	0	1	2	1	2	1	1	1	7	4	1	13	0	1	2
Positive	0	0	0	0	0	0	3	2	0	6	0	8	23	0	0	0
Tubular Changes																
Negative	10	11	3	1	6	0	1	0	0	0	0	0	0	0	1	1
Slight	4	2	1	12	9	3	2	3	1	2	3	1	13	1	3	5
Positive	0	0	0	0	0	0	6	0	0	12	2	9	33	0	0	1
Interstitial Inflammation																
Negative	13	8	1	7	4	2	2	0	0	9	0	0	40	1	2	3
Slight	1	5	2	4	10	1	5	1	1	4	2	1	3	0	1	3
Positive	0	0	1	2	1	0	2	2	0	1	3	9	3	0	1	1
Diffuse Glomerular Lesions																
Negative	13	13	4	12	13	3	5	2	1	4	5	6	6	1	4	6
Slight	1	0	0	1	2	0	3	1	0	3	0	0	7	0	0	1
Positive	0	0	0	0	0	0	1	0	0	7	0	4	33	0	0	0
Focal Glomerular Lesions†																
Negative	13	11	3	12	7	2	4	0	1	2	1	0	2	1	3	3
Slight	0	2	1	0	3	1	1	0	0	2	1	0	3	0	0	2
Positive	0	0	0	0	3	0	0	2	0	0	3	6	1	0	1	1

* Fat stains not made in all cases.

† Includes only the cases not showing diffuse glomerular lesions.

or focal lesions increased the percentage to about 56%. In mild diseases there were no outspoken lesions. The diseased glomeruli tended to lose the delicate markings of the capillary walls and the tufts appeared simpler and more compact. There were thickening of the capillary wall due to thickening of the basement membrane, swelling of cytoplasm of endothelial cells and, in severe cases, an apparent decrease in the number of nuclei in the tuft. The lumen of the capillaries was often narrowed and free of blood. In others it was patent and in some instances distended focally. The content of the

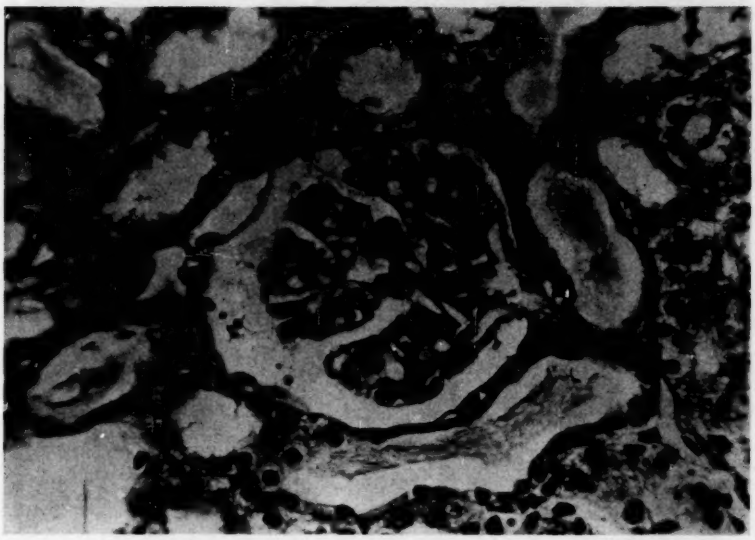

FIG. 6. Rat #108. (Hematoxylin-eosin x 393.) Normal appearing glomerulus. Much proteinuria. Duration of disease 6 days. Albuminuria ++++. No edema or ascites. Serum protein: 4.7 gm./100 cc., NPN: 177 mg./100 cc., cholesterol: 445 mg./100 cc., total lipids, 2200 mg./100 cc.

FIG. 7. Rat #396. (Hematoxylin-eosin x 393.) Swollen walls of glomerular capillaries with homogeneous content. Azocarmine stain showed thick basement membrane. Fat was present in glomerular tuft. Duration of disease 4 days. Massive edema and ascites. Albuminuria +++.

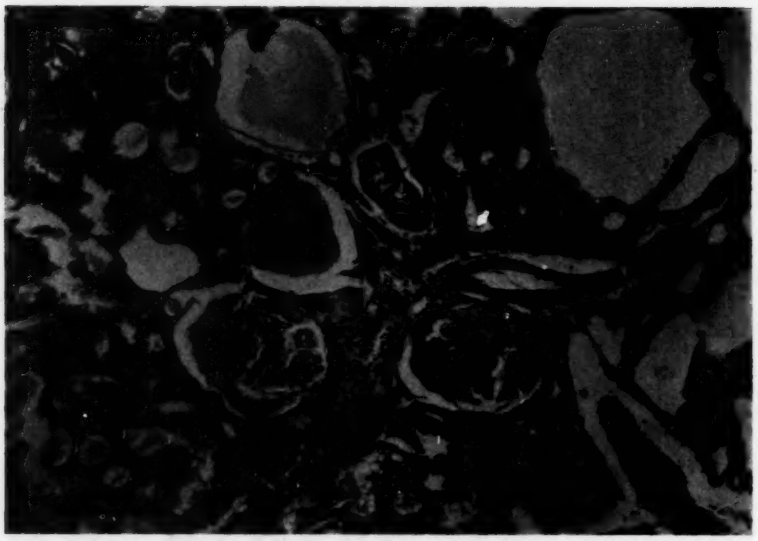

FIG. 8. Rat #199. (Hematoxylin-eosin x 115.) Proliferative glomerular lesions. Duration of disease 10 mo. No edema or ascites. Albuminuria ++++. Systolic blood pressure 140 to 150 mmHg. Serum proteins: 5 mg./100 cc., BUN 80 mg./100 cc., creatinine 1.8 mg./100 cc., cholesterol 165 mg./100 cc. Total lipids 760 mg./100 cc., lecithin 258 mg./100 cc.

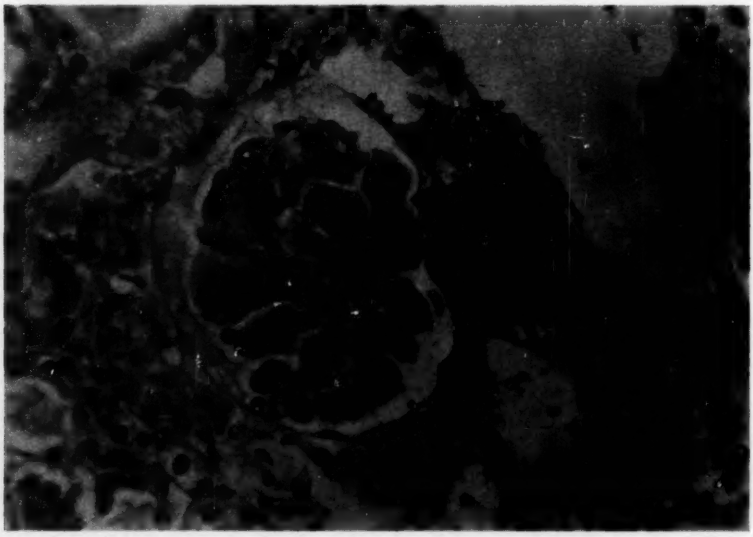

FIG. 9. Rat #393. (Hematoxylin-eosin x 393.) Thrombonecrosis of preglomerular arteriole and glomerulus. Unusually marked and rare lesion. Albuminuria ++. Duration of disease 4 days. No edema or ascites.

capillary lumens was often red blood cells or in other instances a homogeneous coagulum. This was in some instances sudanophilic. This was not directly correlated with demonstrable lipemia in other capillaries. When lipids were present in blood vessels, the intensity of stain was greatest in the glomerular tufts. Frequently cells of the glomerular tuft contained lipid granules whether or not lipemia was demonstrable histologically. In many instances, especially in cases with marked proteinuria, there was a homogeneous fluid about the tuft which occasionally stained for fat. Rarely in severe cases there was necrosis of parts of the tuft and hemorrhage. In a few instances this was associated with a slight exudation of neutrophiles. Proliferation of cells of the glomerulus and capsule

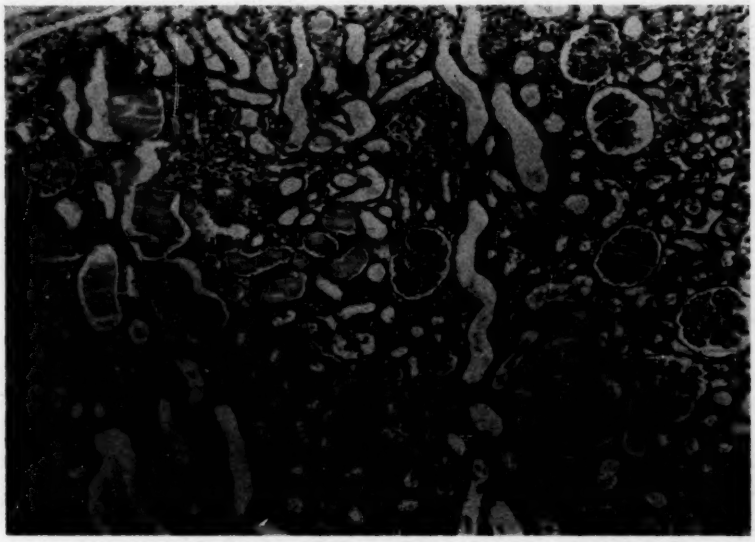

FIG. 10. Rat #274. (Hematoxylin-eosin x 98.) Low-power view showing marked proteinuria. Glomerular lesions are not pronounced. Duration of disease 5 days. Albuminuria ++++. No edema or ascites. Serum proteins 6.65 gm./100 cc., cholesterol 465 mg./100 cc.

occurred rarely in the first week of the disease, but occasionally in the latter part of the first month. Such cases were sometimes associated with swelling of the walls of preglomerular arterioles with fatty degeneration in the media and adventitia. In certain instances thrombosis and necrosis occurred in these arterioles and there was perivascular hemorrhage.

In the late stages the glomerular lesions were not as diffuse and uniform as in the acute stage Thickening of the capillary walls and basement membranes tended to be irregular in distribution. Within the glomerular tuft itself the change was often focal. The lesions of the glomeruli were often characterized by atrophy and progressively increasing proliferation of cells and fibrils in the tuft and capsule with adhesions. Fatty degeneration of the cells of the tuft and capsule was often noted and formed a concentric lamination. Diffuse glomerular lesions were rarely seen in cases of severe disease in the second to fifth months but they were present in 25% of those over six months' duration. Focal glomerular lesions were present in 4 of 5 cases of 2 to 5 months' duration.

The presence of focal glomerular lesions in some of the controls raises the question of spontaneous disease. However, these were slight and, in view of the fact that the glomerular lesions were more prevalent and diffuse in the cases of severe disease as compared with the controls and mild cases, it was concluded that there was a relationship to the disease produced experimentally. Arteriolar lesions in the late stages were not evident.

Tubular Changes: In the early stages tubular changes were largely those of proteinuria in all nephrons (Fig. 10). The protein was progressively more intensively stained as the distal part of the nephron was approached. The most noticeable changes in hematoxylin

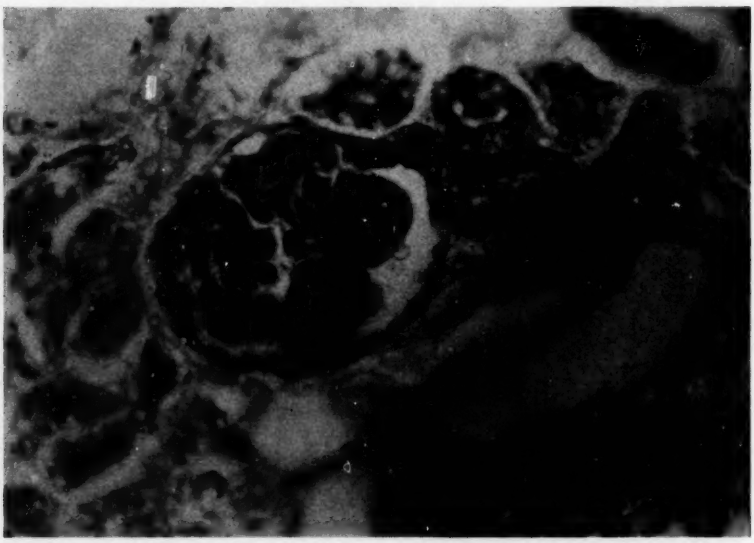

FIG. 11. Rat #204. Sudan-black stain. Lipid droplets in proximal convoluted tubule and in glomerulus. Duration of disease 8 days. Ascites and marked edema. Albuminuria +++. Serum proteins 1.66 gm./100 cc., NPN 225 mg./100 cc., cholesterol 160 mg./100 cc.

and eosin stains was swelling and granularity of the proximal convoluted tubules. The granules had the same tinctorial quality as the content of the lumen. Where the distention of the lumen was marked the cells tended to be flat. The preceding changes were present in all the early, severe cases, although in 25% they were slight. In some of the fulminating cases the tubular lumens were almost empty and the cytoplasm of the epithelium was pale and poorly stained. At first this was considered to be autolysis but later experience in finding it in a patchy distribution indicated that in some instances it was a premortem degenerative change. Necrosis occurred in only a few cases and these were associated with glomerular and arteriolar necrosis. In such cases segments of the proximal convoluted tubules were involved. An exudation of neutrophiles occurred in some of these sites. There was a general parallelism between the tubular and glomerular lesions. It is to be noted, however, that pronounced glomerular lesions occurred occasionally without much proteinuria and, contrariwise, pronounced proteinuria occasionally occurred in the absence of well defined glomerular lesions. Tubular changes increased with the severity of the disease and regressed with the recovery of the animal.

Fatty Degeneration: Fatty degeneration, especially of the proximal convoluted tubules but also of the medullary loops was common, occurring in most of the severe and fulminating cases (Fig. 11). Easily demonstrable fatty degeneration of the tubules and/or glomeruli was present in 50% of the cases. It was present to a slight degree in most of the remainder. The frequency with which fatty degeneration was noted increased with the severity of the disease. It was present in early phases of the disease. In recovered animals it never was seen in any marked degree and thus must regress with the recovery of the animal.

Interstitial Inflammation: Focal infiltration of lymphocytes in the interstitial tissue was seen not infrequently. This was usually associated with focal atrophy of glomeruli and tubules. Inasmuch as it was more prevalent and marked with the severity of the clinical disease and was seen in control rats only occasionally and to a slight degree, it was concluded that it was a lesion related to the nephrotoxic disease. It was uncommon in the early stage and occasionally still seen in recovered animals.

In exceptional instances bacteria were noted in the kidneys, in the acute stage of the disease. They were predominantly in the glomeruli and produced a peculiar local necrosis of glomerular tufts. Abscesses were seen occasionally.

Comment

The renal disease induced in Long-Evans rats simulates lipemic nephrosis with and without glomerular lesions[7] as observed in infants and children almost in every detail. Massive albuminuria develops without a latent period. This is in agreement with results obtained by Smadel, Swift and Farr[2] and represents an interesting difference to the observations made by Kay[8] who noted that "the injection of nephrotoxic duck serum into a rabbit is followed by an interval of several days during which the health of the animal remains unimpaired and the urine shows no abnormalities."

Gross hematuria was not, and microscopic hematuria was rarely and inconsistently, observed. The evaluation of an occasional, not too strongly positive benzidine reaction remains furthermore often questionable, as traces of blood that did not originate in the kidneys may easily mix with the urine.

Marked edema and ascites, associated with hypoproteinemia and hyperlipemia was almost regularly observed in all severely ill animals at onset. The distribution and lability of the edema was strikingly reminiscent of the anasarca seen in nephrotic children. The hypoproteinemia was most marked at onset and slowly improved during the course of the disease which might explain why anasarca was seen only rarely in later stages of the disease. This in turn differs from the frequent observation of improvements and recurrences of edema and ascites observed in nephrotic patients over periods of one to several years. Spontaneous cures were observed in rats after renal disease had lasted from a few weeks to several months, even when no remissions had been previously noted. On the other hand, chronic renal disease has been induced after the initial injection of a nephrotoxic serum that lasted, with or without remissions, for more than 13 months. None of these chronically ill rats of the Long-Evans strain died of renal failure. Some of them might, however, have been killed prematurely. The lack of hyposthenuria, marked hypertension, azotemia or increased creatinine concentration in the blood even in these animals did not suggest an uremic death in the near future. Anemia observed in three of these rats was certainly not caused by loss of blood in the urine. It might have been connected with the persistent, chronic hypoproteinemia.

The frequently noted deaths of rats within the first two weeks, after too large doses

of nephrotoxins had been injected, is without parallelism in the experience of pediatric practice. Marked hypertension, creatinine retention, hematuria or convulsions were not observed in these animals and thus the authors do not believe that uremia was the cause of death. The marked degree of azotemia, which was noted in most of these animals in the absence of creatinine retention and hypertension, might have been of extrarenal origin. Suffocation, due to large amounts of pleural exudates, might have caused death in some of these rats. Further histologic and chemical studies are needed to clarify this question.

In contradistinction to the experience of pediatric practice, intercurrent infections were rarely noted in nephrotic rats. It has to be remembered, however, that these animals were kept continuously isolated in single cages. Their susceptibility to infection with various organisms was not investigated. The question of increased susceptibility to infections in nephrotic rats thus remains unanswered.

The deviations of the blood chemistry associated with the nephrotic disorder in rats were strikingly reminiscent of those encountered in the disease in man.[9] Hypoproteinemia and hyperlipemia involving cholesterol, phospholipids and total lipids, in the absence of creatinine retention, were regularly observed and most marked in the earliest stages of the disease. The marked azotemia noted at onset of most severe diseases, that lead to death within three weeks, is without parallelism in human pathology. Fulminating forms of lipemic nephrosis are unknown in children. Due to the insidious onset of the human disorder, blood chemistry studies are usually not obtained within the first 3 to 5 days after onset. The azotemia subsided in rats that did survive the first few weeks, and thereafter values were obtained that are commonly noted in man.

The blood pressure during the course of the disease in rats showed changes that are in agreement with those observed in nephrotic children. Two-thirds of the animals remained normotensive. Slight and moderate degrees of hypertension were observed in the remaining third. The hypertension usually fluctuated and was not fixed.

The histologic analysis of the renal lesion was of greatest interest as it was obtained in different stages and varying degrees of severity of the disease. The primary lesion occurred promptly after injection of the nephrotoxic serum and was essentially a degenerative one. Glomerular lesions were demonstrable in 73% of the severe cases and in 38% of the moderately severe cases. Protein "leakage" was, however, present in almost all cases except those dying suddenly of shock. Fatty degeneration of the glomerular tuft and capsule and the preglomerular arterioles occurred. The degenerative changes in the tubules were demonstrable in about equal proportion to the glomerular lesions. The changes were usually moderate and consisted of swelling, granularity and fatty degeneration of the cytoplasm. Necrosis was rarely seen. The experiments offered no substantiation or denial of the concept of athrocytosis as explaining the granular change within the cytoplasm. This view, however, can be entertained especially in view of the similar tintorial quality of the protein within the tubules and the protein within the cytoplasm. Following the initial degenerative lesion there was recovery or continuation of the degenerative lesion. Usually there appeared to be at least partial recovery. If recovery did not occur, the degenerative lesion was followed at variable intervals and to a variable extent and degree by proliferative changes in the glomerulus associated with atrophy of the glomerulus and the related tubules. In the Long-Evans strain of rats these changes were not conspicuous and tended to be patchy in distribution. Depending on its degree, it appeared to correspond with the development of hypertension and uremia. This was substantiated by findings in the Whelan strain of rats where there was more con-

spicuous proliferation. Whether the proliferation represents healing of the primary degenerative lesion or is a result of continued abnormal glomerular excretion cannot be answered from the evidence.

The lesions closely resemble those found in children. Where the degenerative change was seen alone there was identity with "pure" nephrosis, and where proliferative lesions supervened, with the "mixed" form. It thus should be pointed out that one and the same experimental procedure may produce the disease in its pure and mixed forms. From these observations and from the work of Pressman,[4] Solomon[10] and Heymann[11] it may be assumed that the primary injury is to the glomeruli and tubules. This is in accordance with findings recently obtained by Metcoff, Kelsey and Janeway[12] in children suffering from the nephrotic syndrome. From a morphologic point of view the histologic disease observed in rats resembles that seen in humans.

Summary

1. Chronic renal disease was produced in 235 4 to 5 week-old rats of the Long-Evans strain by the intravenous injection of nephrotoxic sera obtained from rabbits.

2. Massive proteinuria, largely without hematuria, was noted without delay. Severe edema and ascites was observed in 35% of the animals within the first 2 to 3 weeks. Thirty-two per cent died within the first two weeks. A spontaneous cure of the disease occurred in 30% and chronic renal disease that lasted in some instances as long as 13 months, was observed in the remaining animals.

3. From 125 sick rats, 74% remained normotensive. A fluctuating and moderately severe hypertension was noted in the remaining 26%.

4. The blood chemistry revealed marked hypoproteinemia and hyperlipemia in the earliest phase. This subsided slowly as the disease progressed but did not reach normal values as long as the disease persisted. With a few exceptions the creatinine concentration remained normal during all phases of the disease. Marked azotemia was frequently obtained in severe disease at onset. It subsided regularly within the first two months and slight degrees of azotemia in late stages of the disease were noted in approximately 50% of the rats.

5. A histologic analysis was obtained in 119 sick, 12 recovered and 31 control rats. By correlating the chronologic order of clinical evidence with the pathologic picture, the following conclusions were drawn: (a) The nephrotoxin produces primarily a degenerative lesion with changes in glomeruli and tubules; (b) There may be recovery from the degenerative phase or it may be followed at variable intervals by a variable degree of fibrous proliferation in the glomerular tufts and capsules. Whether this fibrosis of glomeruli is a direct repair of damaged glomeruli or a result of abnormal glomerular function could not be determined; (c) In the degenerative phase the lesion produces the "nephrotic" syndrome. In the proliferative phase, depending on the degree, there are hypertension and uremia.

6. In symptoms and course, in the deviation of the blood chemistry and in the morphology of the renal lesion, this disease in rats simulates the nephrotic syndrome as observed in infants and children. One and the same experimental procedure produces the disease in rats in its so-called "pure" or "mixed" form.

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SPANISH ABSTRACT

Sindrome Nefrótico en Ratas

Enfermedades renales cronicas fueron producidas en 235 ratas entre cuatro y cinco semanas de edad, de la especie Long-Evans, mediante la injección intravenosa de suero nefrotoxico obtenido de conejos.

Se notó inmediatamente la ocurrencia de una proteinuria masiva sin hematuria en la mayoria de los animales. Edema profundo y ascitis se observó en un 35% de los animales en las dos primeras semanas. Curaciones espontáneas ocurrieron en un 30% y el resto de los animales desarrollaron alteraciones cronicas renales, algunas de estas persistiendo por mas de 13 meses.

De un total de 125 ratas afectadas, un 26% desarrollaron una hipertension arterial moderadamente severa de tipo fluctuante. El 74% de los animales permanecieron normotensivos.

Examenes quimicos revelaron una hipoproteinemia marcada con hiperlipemia concomitante en la fase inicial de la afección. Estos valores disminuyeron lentamente con el progreso de la enfermedad, pero nunca volvieron a los valores normales mientras la afección persistió. Con algunas excepciones las concentraciones de creatinina permanecieron normales durante todas las fases de la enfermedad de la mayoria de los animales. Una azotemia marcada fue frecuentemente observada al comienzo de afecciones severas, la cual disminuyó regularmente en los dos primeros meses de evolución, aunque siempre se notó una pequeña azotemia en aproximadamente 50% de las ratas durante las últimas fases de la afección.

Se hizo un análisis histologico en 119 ratas afectadas, en 12 ratas con curaciones espontáneas y en 31 ratas normales de control. De la correlación cronológica de la evidencia clinica y el studio del cuadro patologico, las siguientes conclusiones son derivadas: (a) la nefrotoxina produce primariamente una lesión degenerativa con alteraciones de los glomerulos y tubulos; (b) la fase degenerativa puede desaparecer o puede ser seguida por diferentes grados de proliferación fibrosa de los "tufts" glomerulares y de la capsula, a intervalos variables. No pudo ser determinado si esta fibrosis del glomerulo es una acción reparativa directa del glomerulo dañado o si es el resultado de una funcion anormal glomerular. (c) En la fase degenerativa la lesión renal produce el sindrome nefrótico. En la fase proliferativa se produce hipertension y uremia dependiendo del grado de la lesión.

Esta afección en las ratas simula al sindrome nefrótico de infantes y niños, tanto en sintomatologia y curso de la afección, asi como en las alteraciones de la quimica sanguinea y morfologia de la lesion renal. Las llamadas formas "puras" o "mixtas" de la nefrosis se producen usando el mismo metodo experimental.

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ELECTROENCEPHALOGRAPHY OF THE NEWBORN INFANT

VI. Studies on Premature Infants

By JAMES G. HUGHES, M.D., BILLIE CAMP DAVIS, B.S., AND MARJORIE LEAK BRENNAN, B.A.
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IN RECENT years, there has been an increasing amount of research directed toward a better understanding of the physiology of the premature infant. The attempt has been made to obtain data which would have a meaning in regard to explaining the peculiarities of the premature infant in order that pediatric management might be more effective. Some of these studies have indicated a functional immaturity of various physiologic processes of the premature baby.[1-11]

The present investigators have been especially interested in cortical function of the newborn premature infant as determined by electroencephalography. In previous publications,[12-16] electroencephalography was employed to establish normal standards for full term, newborn infants, studies were made on babies born of mothers given various analgesic agents, and tracings were obtained on full term, newborn infants who evidenced signs of central nervous system damage. However, there have been no previous publications indicating normal standards for brain potentials of newborn premature infants.

It is the purpose of this paper to present what are considered to be normal electroencephalographic patterns of newborn premature infants. The material consists of 31 electroencephalograms on 22 premature infants who weighed less than 2.2 kg. at the time of the first EEG. Twenty-one of these infants weighed between 1.8 and 2.2 kg. at birth, and one weighed 2.3 kg. at birth.

METHOD

EEGs were obtained in a special room adjacent to the premature nursery. Precautions for aseptic technic were employed throughout, caps, gowns and masks being worn by those who handled the babies.

It is understandable that the frail condition of premature infants precluded electroencephalography as soon after delivery as in the studies made previously on full term infants. The authors are anxious to close this time gap between delivery and initial EEG in order to evaluate cortical electric activity as soon as possible after birth.

The tracings were obtained 60 to 90 min. after feedings in order to allow the baby to rest from the nursing process and yet not permit enough time to elapse for the blood to reach hypoglycemic levels. Blood sugar studies were not done, in view of the fact that previous experience[12] had indicated that blood sugar levels obtained shortly after feedings were consistently within the normal range. All babies were bottle fed. Serial runs were taken at intervals that were considered not to be dangerous to the baby's condition.

None of the infants studied were receiving oxygen therapy, oxygen having been discontinued the day before the tracings were obtained.

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All the premature infants were clinically normal and had been born of mothers whose pregnancies, labors and deliveries had been judged to be normal.

Of the 31 EEGs, 24 were obtained while the baby was asleep throughout the tracing, 2 were taken during the wide awake state, and the remaining 5 included variations in alertness in each case from wide awake through drowsiness to sleep.

The machine used was an Offner (Type C 144) 4 channel crystograph electroencephalograph. Standard precautions were employed to assure valid tracings.

Lightweight electrodes 4 mm. in diameter, especially sized for the small dimensions of a premature baby's head, were employed. These were applied to the scalp with electrode paste and bentonite, and covered with small gauze squares. All resistances were below 5000 ohms. In most cases, 6 scalp electrodes were used: 2 frontal, 2 parietal and 2 occipital. The term "parietal" is now used to indicate the same site of the electrode referred to in previous papers as precentral, parietal being the more exact terminology. In some instances, temporal electrodes were also employed. Two

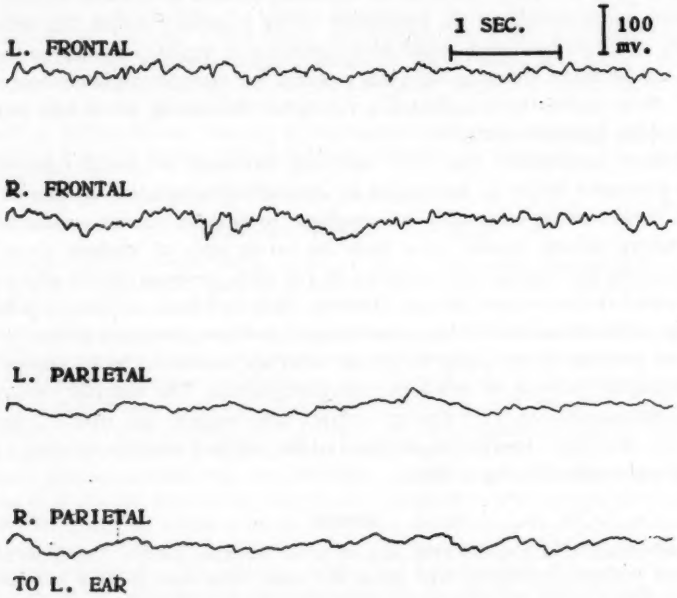

CHART 1. EEG recorded during sleep on 16 day old Negro female premature infant of 8 mo.' gestation who weighed 2.0 kg. at time of tracing.

reference ear-ring electrodes were used. Each run lasted for only 40 to 60 sec., and the leads were changed frequently from 1 pen to another to rule out any possible mechanical differences. The total duration of the EEG was approximately 10 min.

RESULTS

Charts 1 to 3 illustrate sample EEGs of normal premature infants.

In general, all the EEGs showed low amplitude varying from 0 to 40 microvolts. Most of this activity appeared in the range of 7 to 15 microvolts. Occasional microvoltage of 45 to 80 appeared in single wave formation, rarely lasting for more than 1/5 to 2/5 sec. Frequencies ranged from 2.5 to 25 cycles/sec. These fell within three definite frequency bands. The first and rarest were waves of 2.5 to 4/sec. which usually appeared singly at amplitudes of 45 to 80 microvolts. These were commonly of normal sinusoidal conforma-

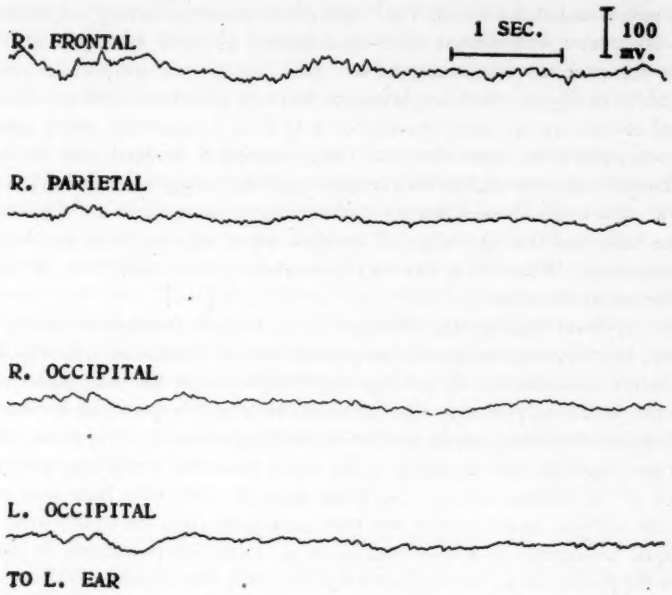

CHART 2. EEG recorded during sleep on 10 day old Negro male premature infant of 8 mo.' gestation who weighed 1.9 kg. at time of tracing.

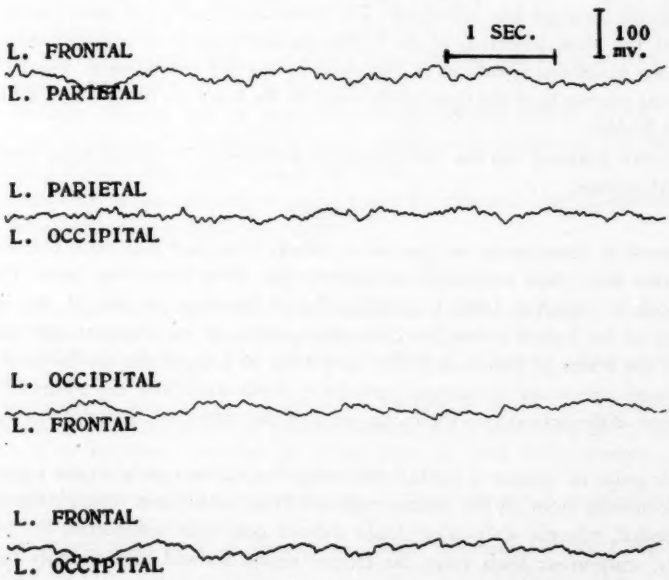

CHART 3. EEG recorded during sleep on 21 day old Negro male premature infant of 8 mo.' gestation who weighed 2.2 kg. at time of tracing.

tion. The second included waves of 5 to 7 cycles/sec., usually occurring in episodes of 1 to 1½ sec. These were well defined and were ordinarily 25 to 40 microvolts in amplitude. The most dominant frequency observed was the 11 to 15 cycle wave which appeared in episodes of ⅗ to 2½ sec., with amplitudes of 10 to 20 microvolts. Between these periods of cortical electric activity were episodes of 0 to 2 or 3 microvolts which appeared as baseline sway, and often lasted for 3 to 10 sec., varying in duration with the individual tracing. This activity often shifted with enough regularity to appear as 1 to 1½/sec. waves, but careful observation showed that the electrode wires swayed with the rhythmic breathing of the baby, and that the height of the slow waves increased with the depth of the baby's respirations. When there was no extracerebral activity exerted on the electrodes, the baseline remained stable.

In the scalp-to-ear tracings, the dominant 11 to 15 cycle frequencies usually occurred in all leads, but they were more constant and rhythmic in the frontal area. The regularity of these waves diminished as the tracings were recorded from the more posterior regions of the brain. In the scalp-to-scalp leads, the amplitude and frequency of the anterior and posterior regions were more nearly equal than was observed on the scalp-to-ear recordings.

When the amplitude and frequency of the waves from the frontal area were compared with those of the occipital area in scalp-to-ear runs, the following facts were noted: In 27 instances, cortical electric activity was more prominent from the frontal area, approximately equal to occipital in 4 cases, and in no instances, less prominent. In scalp-to-ear runs from the parietal areas, the amplitude and frequency were usually less than that of the frontal areas but more than that of the occipital.

In scalp-to-scalp runs, the brain potentials in the frontal-parietal leads were more prominent than that of the parietal-occipital in eight instances, approximately equal in 23, and in no instances less prominent. The observation that in 23 instances of scalp-to-scalp runs, the brain potentials of the frontal-parietal runs were approximately equal to those of the parietal-occipital can be explained by the fact that in such "bipolar" recordings cortical potentials of the more active areas of the brain are being fused with those of less active regions.

In only two instances did the cortical electric activity of the parietal areas equal that of the frontal regions.

Comment

Of interest in these studies on premature infants is the fact that brain potentials from frontal areas show more amplitude and activity than those from other areas. This is not what would be expected from a consideration of histologic studies of the embryonic maturation of the human cortex. To cite only a portion of the literature, the findings of Conel on the brains of babies at birth[17] and those of Langworthy on the fetal brain at various stages late in the gestational period[18–19] demonstrate how far advanced in point of histologic differentiation are the motor areas of the cortex in comparison to the frontal areas.

Another point of interest is the fact that scalp-to-scalp runs show almost equal degrees of electric activity from all the various regions of the cortex from which brain potentials were recorded, whereas scalp-to-ear leads showed noticeable differences. As mentioned previously, scalp-to-ear leads from the frontal region showed more activity than those from other areas.

It was noted that the amplitude of the brain potentials in the scalp-to-scalp leads was

less than that of those in the scalp-to-ear runs. One may wonder whether this is entirely related to the nature of the scalp-to-scalp lead, itself, or whether it might not in part be due to the fact that there is a greater degree of myelination in the deeper structures of the brain late in the gestational period as contrasted to deficient myelination in the cortex at this age.

One point that deserves emphasis is that there have been no studies on premature infants to correlate surface positions of electrodes with the topography of the underlying brain. Such studies are now in progress, but not enough results have been obtained as yet. The authors recognize the possibility that the so-called frontal electrodes might be nearer to the motor area of the cortex of the premature baby than would appear from relative surface positions. This point is now being worked out by thrusting needles through the skulls of stillborn babies at the sites of electrode placement and injecting India ink to mark the cortical sites underlying the various electrode positions. Such studies will show accurately where to place scalp electrodes in order to be certain that they overlie the desired areas of the brain. As regards the present publication, it can only be said that the frontal electrodes were placed over what was carefully considered to be the frontal area of the premature infant's brain.

Conclusions

A report is given concerning normal electroencephalographic patterns of premature infants in the first days of life. Thirty-one EEGs on 22 premature babies constitute the basis of the report.

Three main frequency bands were noted: waves of 2.5 to 4/sec. which usually appeared singly at amplitudes of 45 to 80 microvolts; waves of 5 to 7/sec. occurring in episodes of 1 to 1½ sec. at 25 to 40 microvolts; and frequencies of 11 to 15 cycles/sec. which appeared in episodes of ⅗ to 2½ sec. at amplitudes of 10 to 20 microvolts. The 11 to 15 cycle waves appeared more consistently than did the other frequencies observed, and were usually more prominent in the frontal region.

These findings indicate that in premature infants cortical electric activity from the frontal region is more well developed in regard to frequency, amplitude and rhythm than are the brain potentials from other areas of the cortex.

This observation is contradictory to what would be expected from a consideration of the embryonic maturation of the human cortex.

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SPANISH ABSTRACT

Electroencefalografia en lcs Recién Nacidos. VI. Estudios en Prematuros

Los autores estudiaron las caracteristicas normales del electroencelfalograma en prematuros durante el primer dia de vida. Este reporte se basa en los resultados de 31 electroencefalogramas realizados en 22 prematuros.

Se observó la ocurrencia de tres bandas principales de frecuencia: ondas de 2.5 a 4 segundos las cuales aparecieron separadamente a amplitudes de 45 a 80 microvoltios; ondas de 5 a 7 segundos ocurridas en episodios, a amplitudes de 25 a 40 microcoltios; y frecuencias de 11 a 15 ciclos por segundos, las cuales ocurrian en episodios de 3/5 a 2.5 segundos, a amplitudes de 10 a 20 microvoltios. Las ondas que aparecieron en los 11 a 15 ciclos, fueron mas consistentes que las otras frecuencias observadas y usualmente mas prominentes en la region frontal.

Estas observaciones indican que la actividad cortical de la region frontal de los prematuros, está mas desarrollada en relación a frecuencias, amplitudes y ritmo, que los potenciales electricos originados en otras areas de la corteza. Esta observación está en contradición a lo de esperarse desde el punto de vista de maduración embriologica de la corteza cerebral humana.

University of Tennessee College of Medicine

PREVALENCE OF HEART DISEASE IN TORONTO CHILDREN

1948-1949 Cardiac Registry

By J. H. GARDINER, M.D., AND JOHN D. KEITH, M.D.
Toronto

IN THE city of London, England, in 1936, a registry was set up for the children under the age of 16 years who had rheumatism. This method of appraisal of the problem of rheumatic fever in childhood was a distinct advance over isolated surveys. The organization of the material from this source in the care of the rheumatic child in London was disrupted by the war. In the past five years, attention has again been focused on heart disease in childhood with new surgical technics stimulating an emphasis on the congenital heart abnormalities. From 1941 to 1946 data were collected on heart disease in Toronto school children by simply reviewing the results of routine school examinations. These findings were reported by Keith and Pequegnat.[1] The need for greater accuracy in diagnosis was apparent and stimulated further efforts. Three years ago a registry was organized in Toronto and it was decided to include all forms of heart disease in childhood in its files.

To initiate and maintain the registry a paediatrician trained in heart disease was appointed to the Department of Public Health in the City of Toronto and at the same time he was given an appointment in the cardiac clinic at the Hospital for Sick Children. In this way all the material and facilities of the community in the city of Toronto could be co-ordinated.

PROCEDURE

The cardiac registry was initiated in February 1948 for the purpose of recording useful data regarding heart disease in the children of the city. To make the registry as complete as possible, all available sources were drawn upon. The children attending the 122 elementary and separate schools provided a large proportion of the cases. The 8 general hospitals of the city also provided a useful source of information, as did child health centers, death certificates, cardiac clinics and private patient files of physicians in the city.

In the public schools all children suspected of having any cardiac abnormality or history of rheumatic fever were examined in the school by one of the authors (JG). The parents were generally present at such examination and a history was obtained with reference to rheumatic fever, congenital heart anomalies, german measles of the mother during pregnancy, etc. A detailed inquiry was made regarding the child's exercise tolerance. A clinical heart examination was carried out in supine, sitting and standing positions, blood pressure was taken, note was made of the presence or absence of cyanosis or clubbing. Femoral arteries were routinely palpated. If further examination, such as electrocardiograph or fluoroscopic study, was required, the child was referred to the cardiac clinic of the Hospital for Sick Children, where the authors were able to complete the specialized examination and arrive at a more accurate diagnosis. Selected patients were admitted for catheterization of the heart or angiocardiography when such technics appeared indicated.

With the permission of the family physician, children unable to attend school because of rheu-

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From the Hospital for Sick Children and the Department of Paediatrics, University of Toronto, and the Department of Public Health of Toronto.

This registry was initiated by special contributions from the Rotary Club of Toronto.
(Received for publication Oct. 9, 1950.)

matic fever or cardiac defect were examined at their homes. Children suspected of having heart disease who attended the day nurseries of the city were examined. Information was obtained from child health centres with respect to cardiac defects and it is of interest and importance that 51% of all babies born in Toronto in 1948 were taken to a child health centre at least once. The physician in charge of the registry was notified of all deaths of Toronto residents whenever cardiac disease was recorded on the death certificate. These deaths were followed up by examination of clinical and post-mortem records when such were available or by contact with the physician in charge of the case. Information was culled from the maternity departments, record rooms and pathologic departments of the 8 general hospitals and all cardiac cases in the age group being studied were registered whether the child had been in hospital as a clinic or bed patient for medical or surgical treatment. The larger maternity hospitals were visited to ferret out additional cases. The cardiac consultants in the city added more cases. Registration was carried out for all city residents with rheumatic fever or heart defects who had attended cardiac clinics or were treated as indoor patients at the Hospital

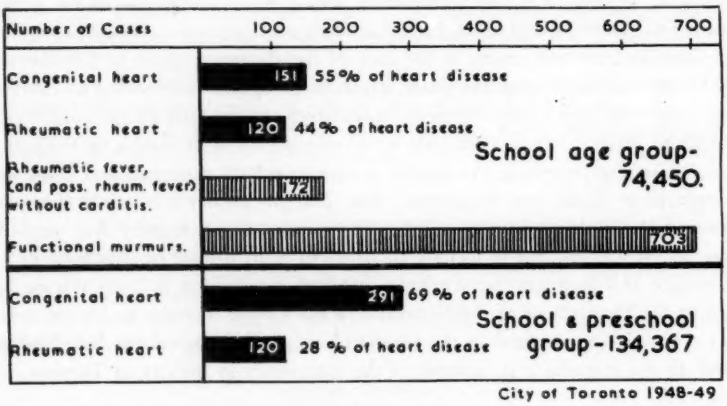

CHART 1. Prevalence of heart disease in Toronto—infants and children.

for Sick Children. Thus, in a city-wide search for heart disease in children, the authors were able to co-ordinate data from a variety of sources.

There were 606 patients examined by fluoroscopy, 29 had catheterization of the heart and 10 were examined by angiocardiography.

RESULTS AND COMMENT

Prevalence—school age cases: A total of 74,450 children in the elementary and separate schools were examined by the school physicians. Of these children, 1,171 were referred for special examination and inclusion in the registry, with a history or clinical findings suggestive of heart disease or rheumatic fever. There was as much interest in removing the label of heart disease as in placing it where it belonged, and it was found that 703 of the referred cases had normal hearts or functional murmurs (chart 1).

There were 274 children who had definite signs of organic cardiac disease. This group represented 0.37% of the school population (table 1).

Rauh[2] in 1938 reported from Cincinnati an incidence of 0.36% heart disease in school children. In 1948 Robinson and Aggeler[3] reported from the San Francisco Cardiac Registry an incidence of 0.44%. Cahan[4] found in 1929, in Philadelphia, an incidence of 0.69% heart disease in the elementary schools.

The 274 cases of cardiac disease were further classified as 151 (or 55% of the 274)

with congenital cardiac defects and 120 (or 44%) with rheumatic heart disease (chart 1). There were 3 acquired nonrheumatic cardiac cases.

Early reviews in the literature reported 10 to 50% of all cardiac lesions in children to be congenital in origin, depending on whether rheumatic infection was prevalent in the particular area being surveyed. Both the Cincinnati Survey and the San Francisco registry found 45% of the cardiac lesions in school children were congenital and 55% rheumatic. The relatively slight difference between their results and those of the present investigators might be explained by the fact that both of the American studies included

TABLE 1

PREVALENCE OF HEART DISEASE IN TORONTO INFANTS AND CHILDREN

	School Age 5–15 yr.		Birth to 15 yr.	
	Total Population—74,450 Cases in Heart Registry—1,171		Total Population—134,367 Cases in Heart Registry—1,324	
	No. of Cases	Percentage of Population	No. of cases	Percentage of Population
Total Heart Disease	274	0.37	423	0.31
Congenital heart disease	151	0.21	291	0.21
Rheumatic heart disease	120	0.16	120	0.09
Other	3		12	0.01
Possibly congenital heart	10	0.015	12	0.01
Possibly rheumatic heart	12	0.016	12	0.01
Rheumatic fever (without carditis)	125	0.17	126	0.09
Possibly rheumatic fever (without carditis)	47	0.06	48	0.04
Functional murmurs	703			

City of Toronto 1948–49.

children of secondary school age, whereas this registry does not include children of that group—in which a large percentage of the cases of rheumatic valvulitis exists.

The Cincinnati report of 12 years ago showed an incidence of 0.15% congenital hearts in the school population and the San Francisco registry two years ago reported 0.2%. The present authors' findings are 0.21% (table 1). The higher percentage of congenital hearts in the more recent reports may be due to increased interest in congenital cardiac abnormalities, which has led to a more intensive search for cases.

There were 172 children who did not have carditis but who presented a history of rheumatic fever or possible rheumatic fever. This group comprised 0.23% of the school population. In San Francisco the figure is 0.3%.

Prevalence—birth to 15 years: From a study of school enrollment, birth and death rates, etc., it is estimated that there are approximately 134,367 children in this city of preschool and elementary school age. Of this number 1,324 are known to the cardiac registry (table 1).

TABLE 2

SEX DISTRIBUTION

	Total No. of Children	Congenital Lesions		Rheumatic Heart	
		No.	Per Cent	No.	Per Cent
Total	134,367	291	0.22	120	0.09
Male		149	51% of 291	61	51% of 120
Female		142	49% of 291	59	49% of 120

City of Toronto 1948–1949.

Four hundred twenty-three children had definite evidence of heart disease. Congenital cardiac abnormalities were found in 291 cases (69%) of those with defective hearts (chart 1). Rheumatic heart disease was diagnosed in 120 cases (28%). There were 12 additional cases of miscellaneous, nonrheumatic cardiac defects.

Sex distribution: Both congenital and rheumatic cardiac disease were practically equally divided among girls and boys. Fifty-one per cent of the cases, in both congenital and rheumatic groups, occurred in boys and 49% in girls (table 2).

Age incidence of heart disease: Congenital heart disease was present in almost twice as many cases in the first year of life as in any other year. After the first year, the distribution was roughly the same for each year (chart 2).

Age incidence for rheumatic heart disease followed the expected pattern. There were no cases under 5 years of age. From 5 years on, the number of cases showed a general increase, with the exception of ages 10, 11, 14 and 15. The failure for the increase to continue through ages 14 and 15 was probably due to the fact that most children of this age are in secondary schools and therefore were not included in the registry (chart 3).

Anatomic diagnosis: Interventricular septal defect was diagnosed in 103 cases or in 36% of those with congenital malformations of the heart. Patent ductus arteriosus was present in 12% while tetralogy of Fallot occurred in 7.2%. The next most frequent abnormality was auricular septal defect which was diagnosed in 5.5%. The 16 most

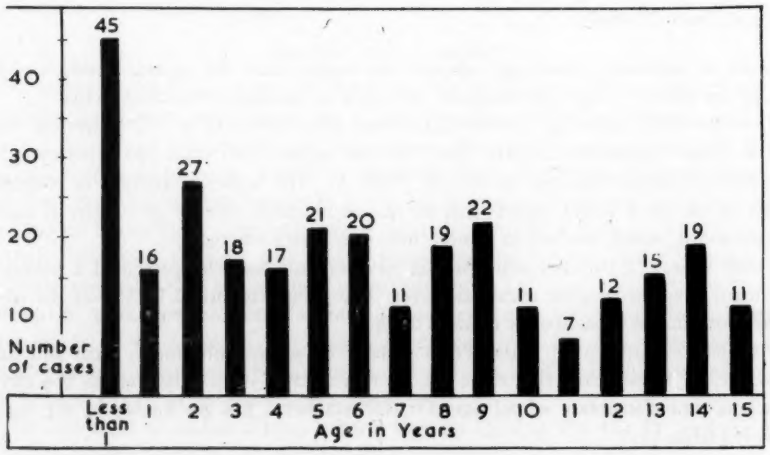

CHART 2. Congenital cardiac lesions—291 cases; age incidence of heart disease.

common abnormalities, listed once according to major defect, are shown in chart 4.

As an aid to accurate diagnosis, 241 of the 291 children were examined by fluoroscopy. Electrocardiographic examinations were carried out when indicated. Twenty-nine children were studied by cardiac catheterization and 10 by angiocardiography.

Of the 120 children with rheumatic valvular disease, 77% had insufficiency of the mitral valve alone. Six per cent demonstrated both mitral and aortic insufficiency, while

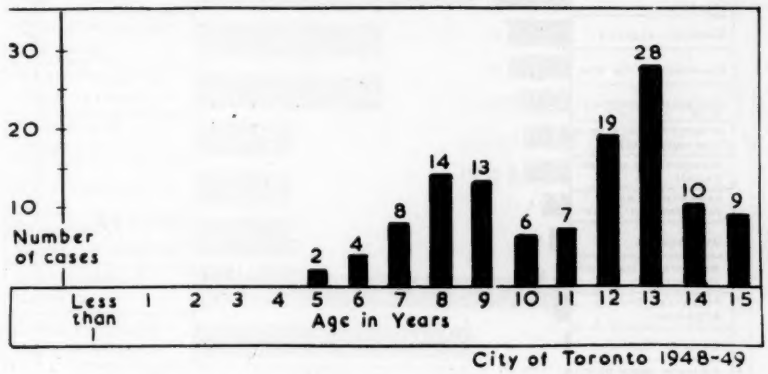

CHART 3. Rheumatic heart disease—120 cases: age incidence.

5% had aortic insufficiency alone. Five per cent showed mitral insufficiency and mitral stenosis and an additional 2.5% had mitral insufficiency, mitral stenosis and aortic insufficiency. The complete list of diagnoses is shown in chart 5.

Mortality studies: In one year (1948) there were 508 children, residents of Toronto under 15 years of age, who died from all causes. Twenty-nine cases, or 5.7% plus 4 possible additional cases, died from congenital abnormalities of the heart. In the same one year period five children died from rheumatic heart disease (table 3).

TABLE 3

CARDIAC DISEASE COMPARED WITH SOME OTHER CAUSES OF DEATH–1948—BIRTH TO 15 YEARS

	Deaths in Age Group	Percentage of Total Group
Total deaths—all causes	508	100.0
Malformations—all types	93	18.3
Congenital cardiac deaths	29	5.7
Probable congenital cardiac deaths	2	0.4
Congenital heart—noncontributory	2	0.4
Rheumatic heart disease	5	1.0
Prematurity	142	28.0
Pneumonia	51	10.0
Birth injury	50	10.0
Leukemia	10	2.0
Cancer—all types	8	1.6
Poliomyelitis	3	0.6
Tuberculosis	1	0.2

City of Toronto.

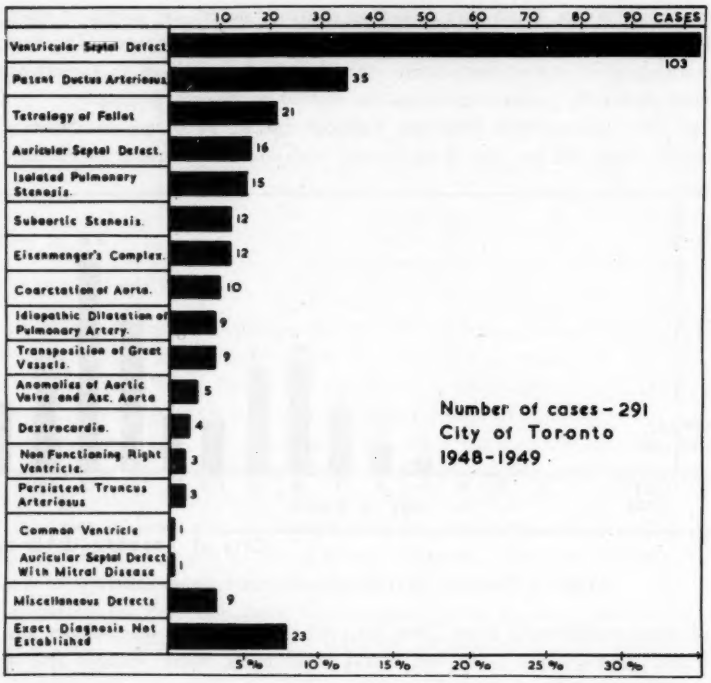
10 20 30 40 50 60 70 80 90 CASES
Ventricular Septal Defect 103
Patent Ductus Arteriosus 35
Tetralogy of Fallot 21
Auricular Septal Defect. 16
Isolated Pulmonary Stenosis. 15
Subaortic Stenosis. 12
Eisenmenger's Complex. 12
Coarctation of Aorta. 10
Idiopathic Dilatation of Pulmonary Artery. 9
Transposition of Great Vessels. 9
Anomalies of Aortic Valve and Asc. Aorta 5
Dextrocardia. 4
Non Functioning Right Ventricle. 3
Persistent Truncus Arteriosus 3
Common Ventricle 1
Auricular Septal Defect With Mitral Disease 1
Miscellaneous Defects 9
Exact Diagnosis Not Established 23
Number of cases - 291
City of Toronto
1948-1949
5 % 10 % 15 % 20 % 25 % 30 %

CHART 4. Frequency of congenital defects (listed once according to major defect).

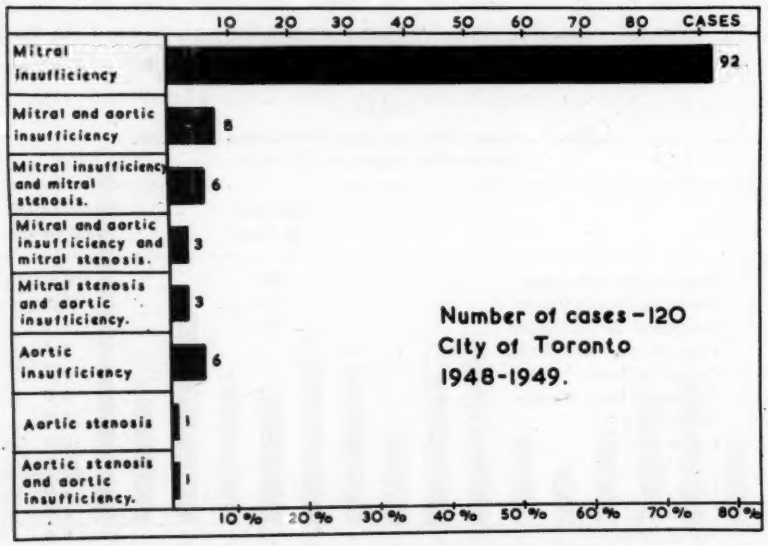
10 20 30 40 50 60 70 80 CASES
Mitral insufficiency 92
Mitral and aortic insufficiency 8
Mitral insufficiency and mitral stenosis. 6
Mitral and aortic insufficiency and mitral stenosis. 3
Mitral stenosis and aortic insufficiency. 3
Aortic insufficiency 6
Aortic stenosis 1
Aortic stenosis and aortic insufficiency. 1
Number of cases - 120
City of Toronto
1948-1949.
10 % 20 % 30 % 40 % 50 % 60 % 70 % 80 %

CHART 5. Frequency of rheumatic valvular disease.

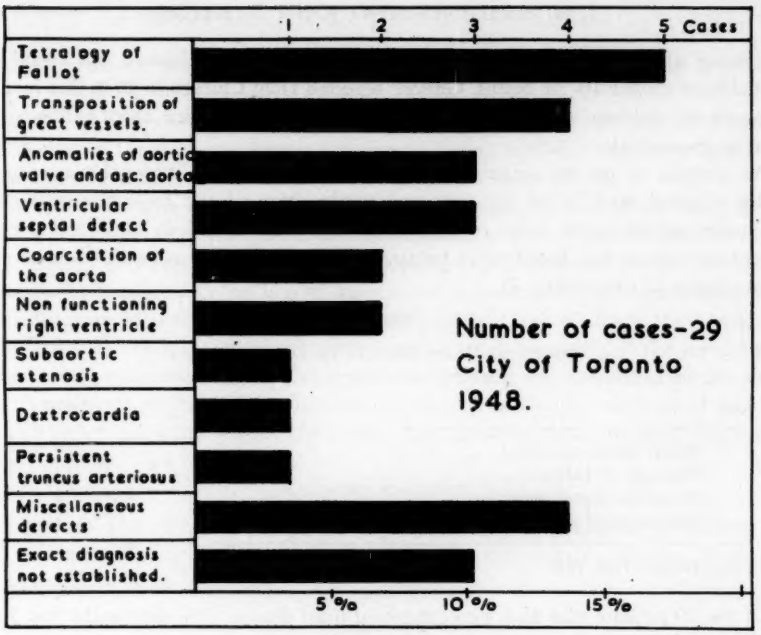

CHART 6. Congenital cardiac deaths.

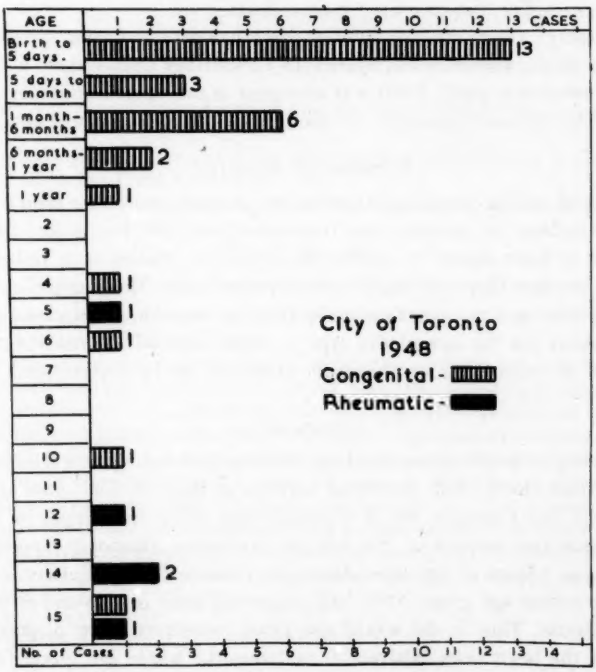

CHART 7. Deaths by ages, congenital and rheumatic.

Epstein[5] of Chicago in 1931 reviewed 1,000 necropsies on children and found congenital heart caused 4% of deaths. Gibson[6] reported from Chicago in 1938 that in 1,950 autopsies on children under 13 years of age 5.4% had congenital abnormalities of the heart or great vessels.

An analysis of the 29 congenital cardiac deaths in Toronto shows that tetralogy of Fallot occurred in 17% of the cases and transposition of the great vessels in 14%. Anomalies of the aortic valve or ascending aorta were found in 10% and a patent ventricular septum was found as an isolated defect and thought to be the cause of death in an additional 10% (chart 6).

TABLE 4

CONGENITAL HEART DEFECTS TREATED SURGICALLY

	Cases
Patent ductus arteriosus	15
Tetralogy of Fallot	12
Ventricular septal defect	2
Coarctation of aorta	1

City of Toronto 1947–1949.

Of the 29 patients who died with congenital heart disease 45% died in the first 5 days of life and 83% failed to attain the age of 1 year (chart 7).

Four of the five deaths due to rheumatic heart disease were children between the ages of 12 and 15 years. The fifth case was 5 years at death.

Cardiac surgery: Thirty resident children have had cardiac surgery performed. In 15 cases a patent ductus arteriosus was ligated. In 12 tetralogy cases surgery was performed. Closure of a ventricular septal defect was attempted in two cases. In one case a coarctation of the aorta was repaired (table 4). Of these 30 children, 27 are still alive.

PURPOSE OF REGISTRY

Registration of cardiac disease as a continuous program provides a fund of knowledge which can be gathered in no other way. It provides good data for judging the prevalence and prognosis of heart disease. It enables the registered children to be followed through the years, to see that they stay under medical supervision. The registry can be used to acquaint the patient and the parents with the facilities available in the school program and in the community for the care of this type of child. General information and methods of prevention of recurrences of rheumatic infection can be disseminated through the registry.

SUMMARY

The prevalence of heart disease in school children in this study was found to be .37%. This agrees rather closely with the recent findings of Rauh in Cincinnati and Robinson and Aggeler in San Francisco, but is a distinct drop from the findings of investigators 20 and 30 years ago, when 1 to 2% was the prevalence commonly reported.

From birth to 5 years of age heart disease in children is almost always congenital in origin. In the school age group 55% had congenital heart disease and 44% had rheumatic heart disease. Thus in the school age group, congenital heart disease occurred in just over half the heart cases, whereas if one takes the whole age group from birth to

15 years, congenital heart disease is found twice as commonly as rheumatic heart disease.

Deaths from congenital heart disease are roughly six times as common as rheumatic heart disease in the birth to 15 years age group. During one year there were 29 deaths from congenital heart disease and five from rheumatic heart disease.

It is of interest that by far the most common congenital defect of the heart is the ventricular septal defect. The patent ductus arteriosus is second with a third as many cases, tetralogy of Fallot is fourth, auricular septal defect is fifth, and so on. This is important to the paediatrician but it is of interest and importance to both the surgeon and the paediatrician to note the frequency according to the cause of death. Here tetralogy of Fallot is first, transposition of the great vessels second, anomalies of the aortic valve and ascending aorta third, ventricular septal defect fourth and coarctation of the aorta fifth. Thus efforts might well be directed to evolving satisfactory methods of treating transposition of the great vessels, the second most common cause of death from congenital heart anomalies.

ACKNOWLEDGMENT

The authors wish to express their thanks to the nurses and physicians of the Department of Public Health of Toronto, without whose co-operation registration of cardiac defects would be quite impossible.

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SPANISH ABSTRACT

La Prevalencia de Cardiopatías en los Niños de Toronto

Se estableció un Registro Cardiaco con el proposito de obtener datos útiles relativos a la prevalencia de cardiopatías en los niños de Toronto, Canada.

Se encontró que la prevalencia de cardiopatías en los niños escolares fué de 0.37%, siendo un 55% debidas a malformaciones congenitas del corazon y un 44% causadas por fiebre reumatica. Se encontró que la incidencia de cardiopatías congenitas fué dos veces mas frecuente que las cardiopatias de origen reumatico, en el grupo de niños entre el nacimiento y los quince años de edad. La mortalidad de las cardiopatías congenitas fué aproximadamente seís veces mas alta que la observada en las cardiopatías de origen reumatico. Entre las causas frecuentes de mortalidad en el grupo de cardiopatías congenitas se destacan en orden de frecuencia: la tetralogia de Fallot, la transposición de los grandes vasos, y en tercer lugar las cardiopatías debidas a malformaciones de la valvula aortica y aorta ascendente. Por esta razon, el autor estima la necesidad de desarrollar metodos satisfactorios para el tratamiento de la transposición de los grandes vasos, la cual representa la segunda causa de mortalidad de las cardiopatías congenitas.

2120½ Queen Street East

ACUTE HEMOLYTIC ANEMIA DUE TO INGESTION OF NAPHTHALENE MOTH BALLS

By JAMES V. MACKELL, M.D., FREDRIC RIEDERS, M.S., HEINRICH BRIEGER, M.D., AND EDWARD L. BAUER, M.D.
Philadelphia

I. Clinical Aspects

(JAMES V. MACKELL, M.D., AND EDWARD L. BAUER, M.D.)

UNTIL recently, ingestion of naphthalene moth balls has not been considered an important factor in the production of acute hemolytic anemia in infants and children. In September 1949, Zuelzer and Apt[1] drew attention to the specific toxicity of moth balls containing naphthalene. These authors reported four cases of poisoning by moth balls, and isolated naphthalene derivatives in the urine of one of them. However, hemolytic anemia following ingestion of naphthalene has been described in the foreign literature[2,3] long ago. This type of poisoning probably occurs more frequently than has been reported.

The hemolytic effect of naphthalene moth balls is well illustrated by the following case, which seems to represent the second one in the American literature in which the hemolytic agent was demonstrated in the urine.

REPORT OF CASE

An 18 mo. old Negro boy was admitted to the children's ward of the Jefferson Medical College Hospital because the father had noted palmar pallor and frequent episodes of crying during the preceding 24 hr. On further questioning, it was ascertained that dark red urine was passed. This had continued until the day of admission. The day before admission, the boy lost his appetite and had fainting spells. There was no history of bleeding, jaundice, vomiting, abdominal pain, constipation or diarrhea.

Physical examination revealed an acutely ill Negro boy with a temperature of 38.1°C., pulse 140/min., respirations 50/min. There was marked pallor of the mucous membranes, palms and soles. Sclerae were icteric. Liver edge was palpable 3 cm. below the costal margin. Spleen was not palpable. The remainder of the examination was normal.

Blood count on admission: Hgb. 2.6 gm./100 cc., 870,000 erythrocytes, 12.2% reticulocytes, 63,000 leucocytes, 438,000 platelets. The differential count was 43% segmented neutrophiles, 1% eosinophiles, 1% metamyelocytes, 33% lymphocytes, 9% monocytes, 13% disintegrated cells, 12 normoblasts and 2 erythroblasts/100 leucocytes. The stained blood smear showed spherocytosis and anisocytosis. Many of the red blood cells were distorted and fragmented; others showed clear colorless areas near the cell border with the hemoglobin concentrated in one portion of the cell (figure 1). No definite Heinz bodies were seen using brilliant cresyl blue stain. Test for sickling was negative. The erythrocyte fragility test was normal. Urine was light orange in color, acid in reaction, negative for albumin and sugar. Microscopic examination showed a few white blood cells. The Van den Bergh test (direct) was negative and the serum bilirubin concentration was 5.3 mg./100 cc. Test for urine urobilinogen was positive in 1:100 dilution. Stool examination was negative for ova and parasites. Benzidine test on the urine 4 days after admission was reported as negative.

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At about this time, the authors' attention was drawn to the work of Zuelzer and Apt[1] which had just been published. Fortunately, it was discovered that the patient's mother was in the hospital in the obstetric ward and she was able to add to the history. On specific questioning, she stated the child was seen playing with moth balls approximately 5 days before he became ill. They were not taken away from him because they were considered harmless. However, he was not observed to ingest them and none were seen in his stools.

The urine had an odor of moth balls. Chemical examination of the urine revealed the presence of alpha-naphthol in large amounts. This continued to be present until the twelfth day after admission. Treatment consisted of whole blood transfusions.

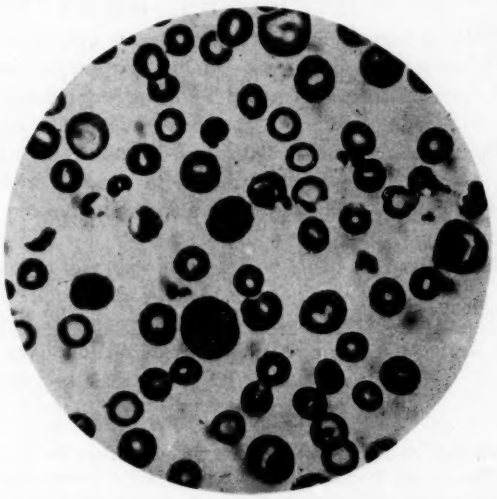

FIG. 1. Blood smear obtained on second hospital day, stained with Wright's stain. Note anisocytosis, spherocytosis and vacuolated areas near red cell borders.

He was discharged in good condition 30 days after admission. At this time, Hgb. was 11 gm./100 cc. and RBC count 4 million/cmm. The serum bilirubin had returned to 0.6 mg./100 cc. (See table 1.)

COMMENT

Most hemolytic anemias are of short duration in infants and yield to blood transfusions. It is rarely necessary to resort to splenectomy. The cause of most of these anemias has been obscure. It is possible that ingestion of drugs or intoxication of another type is responsible for some of these anemias of short duration.

The failure to demonstrate Heinz bodies in this case may be due to the fact that the moth balls had been ingested several days before the first blood examination and severe anemia had already developed. Spherocytosis, fragmentation and distortion of the erythrocytes, and the presence of colorless areas near the cell borders were outstanding features of the stained blood smear.

All the patients reported by Zuelzer were Negro infants about the age of 2 years, as was the patient reported here. The crowded living conditions of Negro families make it more likely that, as the child moves about, he may recover moth balls that have rolled under the furniture and put them in his mouth. It is possible that naphthalene poisoning

TABLE 1

LABORATORY DATA ON BLOOD AND URINE

(Note continued presence of naphthalene derivatives in urine on eighth hospital day, approximately 2 wk. after ingestion of moth balls.)

Day of Hospitalization	1	3	4	6	8	9	12	17
Hemoglobin (gm./100 cc.)	2.60	5.5	6.1		9.3	8.78	9.76	9.3
Erythrocytes (millions)	0.87	1.62	1.98	2.32	3.47	3.3	3.17	3.76
Reticulocytes (%)	12.2	16.7	17.3	19.6	9	7.7		1
Leucocytes (thousands)	63	12.2	12.3		9.5		11.5	7
Platelets (thousands)	438							
Neutrophiles (%)	43	41			53		32	19
Eosinophiles (%)	1	8			1		7	3
Basophiles (%)					1		2	1
Metamyelocytes (%)	1	5						
Lymphocytes (%)	33	22			31		46	60
Monocytes (%)	9	11					2	4
Disintegrated cells (%)	13	12			14		11	13
Normoblasts (no./100 WBC)	12	8						
Erythroblasts (no./100 WBC)	2	6						
Primitive cells (%)		1						
Serum bilirubin (mg./100 cc.)	5.6				0.6			
URINE								
Naphthalene			−		−		−	
Alpha-naphthol			+++		+		−	
Beta-naphthol			++		+		−	
1,2 Naphthoquinone			++		+		−	
1,4 Naphthoquinone			+		−		−	
Benzidine test			−		−		−	
Porphyrins			−		−		−	
Urobilinogen	Pos. 1:100 Dil.							

may be more apt to occur during those seasons when clothes are being removed from or placed in storage, viz., the fall and spring.

The case presented probably would have been classed as Lederer's anemia had the oxidation products of naphthalene not been demonstrated in the urine.

CONCLUSIONS

Naphthalene moth balls are potent hemolytic agents, capable of producing an acute, severe and perhaps fatal anemia. Moth ball poisoning should be suspected in children manifesting evidence of sudden hemolytic anemia, and an attempt should be made to demonstrate naphthalene or its derivatives in the urine. Care should be taken to prevent moth balls from being reached by infants and children.

ACKNOWLEDGMENT

The authors wish to express their thanks to Dr. Leandro M. Tocantins, Associate Professor of Medicine, Jefferson Medical College, for aid in the preparation of this paper.

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II. Hemolytic Action of Naphthalene and Its Oxidation Products

(FREDRIC RIEDERS, M.S., AND HEINRICH BRIEGER, M.D.)

The following metabolites of naphthalene have been noted in the urine: α-naphthyl-glucuronide,[1,2] α-naphthylethereal sulfate,[1] 1-α-naphthylmercapturic acid,[3-5] α-naphthoquinone,[6] dihydronaphthalenes[7] and 1,2-dihydronaphthalene-1,2-diol.[8] A substance yielding free naphthalene on distilling acidified "naphthalene urine"[3,5,9] was identified by Bourne and Young[1,3] as 1,2-dihydro-β-naphthol. Chemical and spectrophotometric examination of the urine in the case of naphthalene poisoning described in Part I of this paper revealed the presence of α-naphthol, β-naphthol, α-naphthoquinone and β-naphthoquinone.

It has been suggested that toxic action is not due to the naphthalene itself but due to its cleavage or oxidation products.[10]

The following five series of experiments were performed in order to determine the relative hemolytic activity of the metabolites, α-naphthol, β-naphthol, α-naphthoquinone and β-naphthoquinone, as well as that of naphthalene itself.

METHODS AND TECHNICS

Individual suspensions of naphthalene, of the naphthols and of the naphthoquinones were prepared in the following manner to allow passage through a sintered glass funnel. One hundred milligrams were triturated with 1 gm. gum acacia and 10 cc. water. The triturate was diluted to 100 cc. with 0.9% NaCl solution. From this stock suspension (1 mg./cc.), the following dilutions were prepared with 0.85% NaCl solution: 1:5 (0.2 mg./cc.); 1:10 (0.1 mg./cc.); 1:50 (0.02 mg./cc.); 1:75 (0.0133 mg./cc.) and 1:100 (0.01 mg./cc.).

Blood specimens were obtained from healthy human donors. These specimens were used within ½ hr. after having been drawn and heparinized. The original hemoglobin content of all the blood specimens was determined by the method of Heilmeyer.[11] The methemoglobin was determined by the method of Horecker and Brackett.[12] Each compound in every dilution was used separately. Controls were used in all experiments.

In Vitro Experiments

Series I: Five cubic centimeters of blood were mixed with 1 cc. of the agents (suspensions of naphthalene, α-naphthol, β-naphthol, α-naphthoquinone and β-naphthoquinone) by gentle inversion for 10 min. The mixtures were placed in a refrigerator at 2°C. for 3 hr. At the end of the incubation period, the plasma which had separated was withdrawn and analyzed for its hemoglobin content.[13]

Series II: Plasma was obtained from 5 cc. of whole human blood by centrifugation at 2100 rpm for 20 min. The plasma was mixed with 1 cc. of the respective agents by gentle inversion for 10 min. The cells were then re-introduced and the mixture was treated as in Series I.

Series III: Erythrocytes from 10 cc. samples of whole blood were washed 3 times with 5 cc. of 0.85% NaCl solution. They were then mixed with 2 cc. of the agents by gentle inversion for 10 min. and incubated at 2°C. for 3 hr. The clear supernatant fluid was analyzed for hemoglobin.[13]

Series IV. Cholesterol 100 mg. and lecithin 100 mg., respectively, were shaken with 5 cc. of the respective agents. After centrifugation at 2100 rpm for 20 min., 2 cc. of the supernatant liquid were withdrawn and used on washed erythrocytes as in Series III.

In all these experiments, the agents were added to the blood at a constant rate.

In Vivo Experiments

Series V: White male rabbits weighing from 3 to 4 kg. were used. Their ears were shaved, and 1, 2, 4 and 5 cc. of each of the agents, in concentrations of 1 mg./cc., were injected into the marginal vein of one ear. At 2, 5 and 15 min. intervals, 5 cc. samples of freely flowing blood were obtained by venisection of the opposite ear. The blood was centrifuged at 2100 rpm for 20 min. and the plasma was analyzed for hemoglobin.[12]

Results

Naphthalene showed no hemolytic activity when added to suspensions of human erythrocytes or when injected intravenously into an unanesthetized rabbit. The metabolites of naphthalene, however, possessed definite hemolytic activity.

In vitro studies showed the hemolytic activity of the metabolites to decrease in the following order: α-naphthol, β-naphthol, α-naphthoquinone, β-naphthoquinone (table 2).

TABLE 2

Hemolytic Effect of Naphthalene Derivatives in Vitro

Compound	Per Cent Hemolysis						
	Concentration in gm./cc.						
	1:1,000	1:5,000	1:10,000	1:25,000	1:50,000	1:75,000	1:100,000
A-Naphthol	74	65	53	46	14	6	<2
B-Naphthol	60	48	32	11	3	0	0
A-Naphthoquinone	18	4	0	0	0	0	0
B-Naphthoquinone	12	<1	0	0	0	0	0

Values are the average of 10 determinations.
Average deviation: 10% of values reported.

In vivo studies demonstrated only α-naphthol to be hemolytic. Fifteen minutes after administration, 6% hemolysis was obtained with injections of 4 cc. (1 mg./cc.), and 9% hemolysis with injections of 5 cc. (1 mg./cc.).

Mixing the agents with plasma before exposing the erythrocytes to naphthalene metabolites did not inhibit hemolysis. The per cent of hemolysis thus obtained was the same as that shown in table 1.

When erythrocytes were washed and then exposed to these agents, the per cent of hemolysis did not change. When the naphthalene metabolites were mixed with cholesterol and lecithin, respectively, and then added to washed erythrocytes, the per cent of hemolysis again remained unchanged.

Methemoglobin was not formed in any of these experiments as far as could be determined.

Discussion

It appears that only the oxidation products of naphthalene cause hemolysis. Thus, naphthalene becomes toxic through metabolic changes after absorption from the gastrointestinal tract. The naphthoquinones are less hemolytic in vitro than the naphthols. β-naphthol and the naphthoquinones are nonhemolytic when injected intravenously. Hemolysis in vivo is caused by α-naphthol.

Experiments II, III and IV were made to determine whether plasma, cholesterol or lecithin has any deactivating effect on the agents. Such a protective mechanism is observed in the case of saponins and surface-active agents. Hemolysis was not decreased in Series II and IV, nor was it increased in Series III. Thus, plasma, cholesterol and lecithin have no effect on the hemolytic power of the toxic agents. However, the experiments on rabbits showed that the hemolytic action of the metabolites of naphthalene is attenuated in vivo.

Naphthoquinones are fairly strong oxidizing agents. Their normal oxidation potentials (E_o) are -0.47 volts for α-naphthoquinone[14] and -0.55 volts for β-naphthoquinone.[15] Nevertheless, no formation of methemoglobin was observed in vitro or in vivo. This observation and the fact that naphthoquinones showed much lower hemolytic power in vitro than the naphthols and that they did not cause hemolysis in vivo suggest that the naphthoquinones are rapidly deactivated. Metabolic attack, especially biologic oxidation of polycyclic hydrocarbons, is not a simple substitution process. It may differ radically from chemical substitution in vitro.[16] It is unknown whether the naphthoquinones are intermediates in the formation of naphthols or whether they are formed from the corresponding naphthols and then destroyed rapidly in the organism.

Summary

α- and β-naphthol and α- and β-naphthoquinone were found in the urine of a child suffering from severe hemolytic anemia due to ingestion of naphthalene moth balls. The hemolytic properties of naphthalene, of the naphthols and naphthoquinones were examined in vitro and in vivo (rabbits).

Naphthalene itself was found to be nonhemolytic in vitro or in vivo. The hemolytic power of the naphthalene metabolites in vitro decreased in the following order: α-naphthol, β-naphthol, α-naphthoquinone, β-naphthoquinone.

Hemolysis due to α-naphthol was observed in vivo (rabbits). However, its hemolytic action was significantly weaker than in vitro. β-naphthol and the naphthoquinones showed no hemolytic activity in vivo (rabbits).

Plasma, cholesterol and lecithin did not inhibit the hemolytic activity of the naphthalene metabolites in vitro.

Formation of methemoglobin was not observed.

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SPANISH ABSTRACT

Anemia Hemolitica Aguda Debida a la Ingestion de Bolitas de Naftalina

Se estudia un caso de intoxicación por bolitas de naftalina de un niño de raza negra de 18 meses de edad. El cuadro clínico fue el de una anemia hemolítica grave con esferocitosis, fragmentación de eritrocitos y zonas incoloras cerca de los bordes de estas células. Se demostró la presencia en la orina de α-y β-naftol y α-y β-naftoquinona.

El naftaleno no mostró ser por sí hemolítico *in vitro* o *in vivo* en el conejo.

El poder hemolítico *in vitro* de los metabolitos del naftaleno decrece en el siguiente orden: α-naftol, β-naftol, α-naftoquinona,, β-naftoquinona.

El α-naftol produjo hemólisis *in vivo*. Su acción hemolítica fué, sin embargo, más débil que *in vitro*. El β-naftol y las naftoquinonas no mostraron acción hemolítica *in vivo*.

El agregado de plasma, colesterol o lecitina no inhibió la acción hemolítica de los metabolitos del naftaleno *in vitro*.

No se observó formación de metahemoglobina.

Jefferson Hospital

Pediatrics

VOLUME 7 MAY 1951 NUMBER 5

AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

THE PRESIDENT'S PAGE

THE latest Academy directory has been sent to the membership. I want to call your attention to the first part of this directory. The first few pages are taken up with the district and state chairmen. These are important in a democratic organization such as ours. Note the name of your state chairman and give him your cooperation in whatever he is doing. He was elected to that office and wants your ideas. Note the name of your district representative, for he was also elected, and by reason of this office is a member of the Executive Board which is the governing body of the Academy.

If you turn to page 9 and following, you will note some changes in committees. This is an attempt at clarification, based on some of the recommendations of the Reorganization Committee which was appointed by Dr. Sisson when he was President. The standing committees were the suggestion of that committee and are seven in number.

The Advisory Committee for Child Health is a purely advisory committee. It has no power except to render an opinion for the Executive Board. Its chairman is the immediate past president and its members are, in almost every instance, chairmen of other Academy committees. Ex officio members of this committee are the Scientific Program Chairman and the Editor of PEDIATRICS and of course the President. This gives the Executive Board, through the President, the collective opinion of those that are particularly well acquainted with the several areas of work in which the Academy interests itself. It is in effect a cabinet for the President.

The Liaison Committee suggests to the Board the organizations with whom we have mutual interests and with whom working relations should be established. It is also their prerogative to suggest appropriate members who could be made our representatives to such groups.

The Legislative Committee keeps the Board informed on pertinent legislation. The Publications Committee has charge not only of the business side of PEDIATRICS but of all publications put out by the Academy or any of its committees.

The Scientific Program Committee has as its chairman a member who is paid a nominal sum and who works the year round at his task. His work has been described in an earlier letter. This committee works in cooperation with the Scientific Exhibits Committee. These two committees have charge of the annual meeting only.

The Awards Committee includes a representative from each of the eight districts in

the United States and chooses the winner of the Borden Award and of the two Mead Johnson Awards. These papers are a part of the Annual Meeting.

It is the duty of the Nominating Committee, through its representatives in each of the nine districts, to canvass all the state chairmen to get an opinion of the wishes of the membership within their states as to who should be nominated for President-elect. Each state chairman consults his membership and reports to the member of that committee for his district.

The organizational committees include, first, the Public Relations Committee. This is not a publicity committee but is primarily concerned with better public relations among our membership. It also is deeply concerned with good public relations with other voluntary organizations and foundations working with children and youth, with governmental organizations working with children, and with commercial firms whose good will is one of our great assets.

The Budget and Finance Committee presents a budget to the Board, and it is their concern to see that each division of the Academy that is allocated funds lives within its budget.

The Committee on Latin American Affairs is concerned with anything that has to do with fostering good relations with the membership of District 9. Medical scholarships and fellowships for Latin Americans is one of their projects.

The Committee for Geographical Distribution of Physicians is chiefly concerned with placing pediatricians in the smaller communities. The Committee for the Care of European Children is affiliated with the national organization of the same name. It aids in the examination of children from Europe who need medical care. It functions at the different ports of entry on the east coast of the United States.

Another activity of the Academy which should be mentioned here, even though it is not a committee, is a registry which has been taken over by the central office. It is a clearing house by which any hospital that desires a pediatric resident can write in and get the names of available candidates. As a corollary of this, any student desiring a pediatric residency can write to the central office and receive a list of possible openings in hospitals.

At a later time I will discuss the work of the scientific committees because there is not room here, but it is my feeling that many members do not know the intent of the standing and organizational committees, and a synopsis of this sort would interest you more in the fields which our organization covers.

PAUL W. BEAVEN, M.D., *President*

Pediatrics

VOLUME 7 MAY 1951 NUMBER 5

SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

AN OPEN FORUM

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

DEAR DR. HARPER:

George Wheatley's letter reminding us of the frightful toll of child life exacted by accidents prompts me to mention a practice I have tried to make routine. Probably many other Academy members have done about the same. The one year check-up, practically universally practiced by pediatricians, is a strategic time to bring up the danger of accidents which are so frequent in the preschool period. Before giving the routine booster of triple vaccine and tuberculin test, I like to make a point of reminding the mother that her child has safely passed one of the most dangerous periods of life—the first year. I believe it impresses the mother when I tell her that from now on the principal danger to her child is not poliomyelitis, not scarlet fever, diphtheria, whooping cough or pneumonia, but that if she should lose her child, it is more likely to be through accidental injury. She is reminded that many household cleaning powders and liquids may fatally poison her child or horribly disfigure him, that a few aspirin tablets or two or three of grandmother's heart pills might kill him. This statement is reinforced with the true statement that I have seen children die from exactly these causes. She is told that boric acid and oil of wintergreen are deadly poisons in much smaller amounts than most people realize; that unguarded basement stairs can be death traps; and that peanuts and popcorn are not suitable for the preschool child. Few parents know that berries of the common yew evergreens, the gimson weed, the wild sweet pea, and the castor bean are poisonous. I suggest that she return home and "police" the house to remove the "booby traps" from her child who will soon be walking and climbing all over the home.

The prevention of accidents at all ages has become an important public health problem. Pediatricians must put preventive practice in this field right along with our programs to cut mortality from prematurity and rheumatic fever. I think that George Wheatley's idea to have a book on accident prevention to hand to parents is a good one.

E. H. WATSON, M.D., *Ann Arbor, Mich.*

TRENDS

By JOHN P. HUBBARD, M.D., *Contributing Editor*

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

THE following two contributions deal with the activities and services of official agencies in the field of child health and their relationships to the practicing physician. Dr. Clarence H. Webb, writing as Liaison Officer from the American Academy of Pediatrics to the Children's Bureau, reports on the replies from the State Chairmen to a questionnaire asking for an appraisal of the relationships between pediatricians, state departments of Maternal and Child Health and the Children's Bureau. Dr. Reginald A. Higgons, in his position as Regional Chairman in Pediatrics for Region No. 3 of the Medical Society of the State of New York, reports on the results of an inquiry as to the value of child health conferences and the attitudes of the practicing physicians to such services in New York State.

* * *

STUDY OF RELATIONSHIPS BETWEEN ACADEMY MEMBERS, STATE CHILD HEALTH AGENCIES, AND THE CHILDREN'S BUREAU

By CLARENCE H. WEBB, M.D.

During the past year each state chairman of the Academy was asked to give an appraisal—preferably after consulting his members—of the relationships existing between pediatricians, state agencies which direct Maternal and Child Health and Crippled Children's Services, and the Children's Bureau. This study was prompted by the belief that all of these groups were working toward a common goal of improved child health, that conflicts had arisen largely over methods or fields of activity, and that these differences were not insurmountable but might be resolved after frank recognition and discussion. These matters had been fully discussed with Academy members and officers, likewise with officials of the Children's Bureau.

Additionally it was deemed of interest to the membership to secure some information concerning the development of state programs and plans to meet needs demonstrated by the Academy's Study of Child Health Services. An inquiry, approved by President Shaw, sought a reply from each State Chairman to the following questions:

1. How satisfactory is the working relationship between the pediatricians of your state and the agencies which direct Maternal and Child Health and Crippled Children's Services?

2. What criticism of the way these services are conducted, of the policies of these state agencies or of the Children's Bureau, on the state or national level?

3. What suggestions do you have to offer concerning improvement of State Maternal and Child Health and Crippled Children's Services?

4. As a result of the Study of Child Health Services in your state, are there child health needs which the Children's Bureau, the state agencies, pediatricians and citizen's

groups should be endeavoring to meet by joint action, financial assistance or more intensive study?

Answers were received from the chairmen of 43 states, Hawaii and the District of Columbia. In eight instances, reports indicated that opinions had been received from a large cross-section of the state membership, and specific opinions of 22 Academy members in Illinois, 14 in the District of Columbia and 31 in Louisiana were available to me. Although the questions were not as concisely stated as might have been desirable (in an attempt to avoid a discouragingly lengthy questionnaire) and some chairmen hesitated to speak for their membership, most of the answers evidenced thoughtful consideration. All shades of opinion were expressed; the pros and cons on any question showed no regional imbalance or bias, and therefore the results are considered to be representative of the present thinking within the Academy membership. The present article summarizes the more extensive report submitted to the Board and State Chairmen; it is obviously impossible in a brief summary to quote all opinions, but representative expressions can be given.

I. Relationships Between Pediatricians and State Agencies

Thirty-one of the 45 chairmen described this relationship as pleasant, cooperative, good, excellent, satisfactory or harmonious. Three others described it as "only fair," "good, but not cooperative" and "cooperatively but in a small way." Three midwestern chairmen reported good relationships with the Maternal and Child Health Agency but less satisfactory with Crippled Children's Services; the reverse situation was reported from two southern states. Of the remaining six chairmen, one made no comment, four indicated a lack of mutual interest and one indicated that the scarcity of pediatricians in the state precluded cooperative activity. It was evident that satisfactory or unsatisfactory relationships had no regional distribution but often depended on personalities involved within the given state.

Exceptionally good programs have been developed on a cooperative basis in some states. In Maryland the Director of Maternal and Child Health and Crippled Children's Services of the State Health Department is secretary of the Committee on Infant Care of the State Medical Society; this committee is composed largely of Academy members and is quite active within the state. In North Carolina the premature program is financed by the Children's Bureau, administered by the Bureau of Maternity and Infancy of the State Health Department and has an advisory committee from the state chapter of the Academy. The Ohio Maternal and Child Health Service maintains close relationship with Academy members through an advisory board, consulting pediatricians before instituting programs. Through similar liaison committees with state medical societies or pediatric societies, cooperative planning and action are reported as very effective in Michigan, New York, Washington; in Hawaii, representatives of governmental agencies, professions and the public coordinate their efforts through the Oahu Health Council. Several chairmen state that relationships between practitioners and state agencies are improving progressively as a result of cooperative activity during the Academy study.

II. Criticism of the Services and Policies of the State Agencies or the Children's Bureau

(a) State Agencies. Fifteen of the 45 chairmen had no criticism to offer; eight failed to answer or stated that they had inadequate data; six voiced the desirability of improving

relationships by the development of advisory committees, more frequent conferences, improved public relations and increased use of pediatricians by the agencies. Impractical recommendations due to failure to consult practitioners, injection of personalities into state policies, and internal strife within the state agencies were handicaps mentioned by three chairmen.

Specific objections were: too large patient volume in clinics; failure to confine services to those unable to pay; inadequate compensation to pediatricians (in comparison with orthopedic fees); control of policies and services for crippled children by orthopedists; acceptance for crippled children's services only for complete care and refusal to allocate funds for crippled children not under control of the agencies. Academy members from Illinois and Louisiana who have worked with the agencies also mention: "red tape," "manufactured work because of too much overhead," inadequate screening, failure to recognize local problems, patients or reports not returned to referring doctors, solicitation of private patients, inadequate social service.

(b) Children's Bureau. Many chairmen did not mention the Bureau specifically. Ten believed that the Bureau favored governmental control of medicine; several of these quoted a former associate chief of the Bureau to document this opinion. One chairman had no complaint with planning at the Federal level, but objected to the tie-in of this planning with power exerted through Federal funds. A second voiced objection to attempts to dictate policies within the state through control of allocated funds; a third expressed doubt that a satisfactory relationship between the Children's Bureau and his members could be effected.

Conversely, chairmen of two states report no criticism of the Bureau in recent years; a third states that the Bureau has always been helpful in his state. Following a recent meeting of Academy members in one state, where these matters were discussed fully, the chairman reports that pediatricians there "feel more kindly toward the Children's Bureau—because they feel that the Bureau's stand on State Medicine has changed considerably in the past few months." A similar opinion was expressed by a number of the members from Illinois and Louisiana. The chairman of another state believes that the suspicion engendered by open advocacy of governmental control of medicine by the Social Security Administrator is reflected upon the Children's Bureau and all other agencies under his control; that all health services in the Federal Security Agency would have better relations with the profession if this situation could be changed.

III. Suggestions for Improvement of Maternal and Child Health and Crippled Children's Services

Many constructive ideas were offered in addition to correction of the previously listed criticisms. One-third of the chairmen considered state-wide consultation and planning between agency directors and practicing physicians to be a paramount need. Publicizing of the agencies' plans and programs among the profession and in medical schools would enable physicians to use and cooperate with the program.

Another large group mentioned increased state finances as a need, either to match federal funds or to develop services independently. Personnel needs were cited in a number of states, especially for individuals with pediatric and other specialized training; the opinion was expressed that professional relationships would be enhanced if more executive positions were filled by persons with pediatric training.

New or expanded programs for rheumatic fever, prematures, school health, child guidance, mental hygiene, tuberculosis, speech training, hearing and visual defects, convalescent care, education and vocational training of crippled children (especially cerebral palsies) were listed as special needs in various states.

IV. Joint Action, Financing and Study of Child Health Needs Demonstrated by the Study

This question elicited a wide range of opinions. Many chairmen referred to their state report, wherein specific needs and plans were outlined. Quite a number indicated that cooperative programs resulting from the study were satisfactorily in progress between pediatricians, state and Federal agencies. In other instances, opinions were about equally divided as to use of Federal funds to finance state programs, although financial difficulties were often anticipated unless these funds were used.

Many states demonstrate increased activity within pediatric organizations as a result of the study. The Montana State Pediatric Society was recently formed as a result of a state-wide School Health Meeting. Academy members in Illinois expressed the opinion that a state organization of Academy members would enable them to maintain better acquaintance with state-wide health problems and pediatric agencies.

Numerous special programs were listed as worthy of cooperative planning and financing. Some of these have been listed under Question III; additionally, there might be mentioned: state funds for hospitalization of indigent children; care of epileptic patients (especially of normal or superior intelligence); increased pediatric training; dental services and school health programs.

Only a few pessimistic opinions were voiced; one chairman questioned the value of the Study of Child Health Services in his state; another questioned the desirability of holding the White House Conference because of war conditions. A third thought that agencies within his state should avoid new programs or expansion, but expressed a need for constructive coordination of local and state agencies.

Summary

It has been refreshing, as Liaison Officer of the Academy, to have this opportunity of sampling the varied experiences and opinions of Academy members. I am impressed with the fact that American pediatrics is not static, but is wide awake, thinking and acting. There are evidences that the Academy study stimulated this awareness of pediatric problems among its members.

In most states the relationships between pediatricians and state agencies are satisfactory, but generally can be improved by mutual education and understanding, which could be sought by regular consultation. State-wide planning, trained personnel and enhanced funds appear to be primary needs if improved child health is sought on a state-wide basis. There is a prevailing opinion that national planning and consultation are helpful, but that establishment of policies and control of funds should preferably proceed on the state level. There are evidences that relationships between pediatricians of this country and the Children's Bureau are improving, but old suspicions and current misunderstandings should be discussed very frankly. If attitudes of suspicion and tendencies to work at cross purposes are eliminated, and if proper fields of endeavor are recognized, I believe that there exists today an excellent opportunity for the pediatric practitioners and teachers, the

state agencies and the Federal agencies to work cooperatively toward their common goal of improved health for infants and children.

Dr. Higgons has summarized in a letter an article published in the *New York State Journal of Medicine,* under the title of "Relationship of Child Health Conferences to the Private Practice of Medicine":[1]

"At the suggestion of Dr. Paul Beaven, I am writing you with regard to an article which I wrote and which was published in the *New York State Journal of Medicine.* I was asked to investigate this matter by the Public Health Division of the New York State Medical Society for presentation at the Annual Meeting of the Society in New York before the section on Public Health, Hygiene and Sanitation, held May 11, 1950. In order to obtain the necessary information for the presentation, I prepared a questionnaire consisting of the following seven questions:

1. Do you believe that the well-baby stations serve useful purposes?
2. Do you believe that the immunization program of these stations is a proper public health service?
3. Do you approve of the means test used by the Department of Health to decide which babies will be followed routinely for preventive pediatric supervision (mother, father, and two children, with incomes up to $3,500)?
4. Do you agree with the principle that no babies should be treated for any pathologic condition other than a minor feeding problem in the well-baby station?
5. Have you personally had any babies referred back to you for correction or treatment of conditions discovered in the well-baby stations?
6. Do you feel that the well-baby station is a justifiable public health education modality?
7. Do you feel that such public health education has a tendency to increase the demand for pediatric care by the private practitioners?

"I then sent this questionnaire to 76 practitioners in Westchester County who had indicated to the County Medical Society that they had a special interest in child care. Many of them were not full time pediatricians.

"I was very much interested to find that 86% of the questionnaires were filled in and returned, and that of the 420 questions answered, 77% were in the affirmative. The actual number of affirmative answers percentagewise to each of the seven questions was as follows:

Question 1	95%
Question 2	90%
Question 3	76%
Question 4	92%
Question 5	46%
Question 6	88%
Question 7	71%

The answers to #3 were 24% (13 individuals) negative, but seven of these added supplemental remarks which varied from a feeling that the means test was not rigid enough, to the reverse that it was not flexible enough.

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[1] New York State J. Med. **51**:355 (Feb. 1) 1951.

"The answers to question #7 surprised me and I feel that the negative answers were based upon lack of education as to the true import of the question which suggests that more propaganda along this line might be indicated.

"The negative answers to question #5 should, I think, be discounted as it appears, after talking to some of the health department pediatricians, that babies are frequently referred back to their doctors for treatment but apparently neglect to tell the physician that the Child Health Conferences referred them.

"I am pleased to note that many of my personal convictions acquired through years of pediatric practice have been substantiated by the replies to this questionnaire. If we can take this sampling as representative of the physicians of the State, it would appear that the child health conference system may expect to have the continued support of a majority of the practicing physicians."

NEWS AND ANNOUNCEMENTS

Twenty medical scientists have been named as the fourth group of "Scholars in Medical Science" appointed by the John and Mary R. Markle Foundation as part of its program to keep young doctors on medical school teaching and research staffs, John M. Russell, executive director of the fund, announced yesterday. Mr. Russell also announced the decision of the Board of Directors to increase the amount of the grant $1,000 a year, making the 5 year total $30,000 instead of $25,000. Beginning July 1, this increase will also apply to the 46 current grants made during the first 3 years of the program. All grants will be made direct to the medical schools at the rate of $6,000 annually, earmarked for support of a specific doctor and his research. Under the program a total of 66 doctors on the staffs of 39 medical schools in the United States and Canada will be aided, with grants amounting approximately to $1,900,000.

Among 20 Scholars whose appointments begin in 1951 are 2 pediatricians: (1) Henry T. Bahnson, M.D., resident and instructor in surgery, The Johns Hopkins University School of Medicine (B.S., Davidson College; M.D., Harvard Medical School). Surgery: cardio-respiratory physiology. Grant to The Johns Hopkins University School of Medicine. (2) Robert E. Cooke, M.D., resident and instructor in pediatrics, Yale University School of Medicine (B.S., Yale University; M.D., Yale University School of Medicine). Pediatrics: physiology of metabolic disturbances in children. Grant to Yale University School of Medicine.

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The Cook County Graduate School of Medicine announces The Two Week Personal Course in Cerebral Palsy which will be held July 9-21, 1951. Communications should be addressed to the Cook County Graduate School of Medicine, 427 S. Honore St., Chicago.

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The Third Panamerican Congress of Pediatrics, American Academy of Pediatrics, Latin American Division, District IX, will meet Dec. 5-8, 1951, in Montevideo, Uruguay.

Officers are as follows: President: Dr. Conrado Pelfort; Vice Presidents: Drs. Julio A. Bauza and Prof. Victor Escardo Y Anaya; Secretaries: Dr. Prof. Maria Luisa Saldun de Rodriguez; Treasurer: Dr. Hector C. Bazzano; Members: Dr. Prof. Euclides Peluffo and Dr. Prof. Julio R. Marcos.

Subjects to be discussed: 1. Rheumatic Fever; 2. Blood Diseases of Hemorrhagic Tendency; 3. Surgical Treatment of the Congenital Malformations; 4. Parasitary Diseases of Social Importance in the Child; 5. Teaching of Pediatrics; 6. Mental Hygiene and Neurosis in Childhood.

On Dec. 2-4, 1951, the Third South American Congress of Pediatrics will also be held in Montevideo.

For further information write to the Office of the Secretary, Av. 18 de Julio 1246, Montevideo, Uruguay.

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The following diplomates were certified by the American Board of Pediatrics, Inc., at New Orleans, March 2, 3 and 4, 1951:

Allen, Elaine Louise, 1430 Tulane Ave., New Orleans.
Baker, Julia, 2a Campos Eliseos, Mexico, D.F.
Bauman, Donald Frederic, 404 Chapman Bldg., Fullerton, Calif.
Black, Robert J., Harbin Clinic, Rome, Ga.
Brakel, Carl Arthur, 617-619 Fernwell Bldg., Spokane, Wash.
Branch, George R., 4325 Cole Ave., Dallas.
Burke, Daniel Wilbern, Jr., 956 Dauphin St., Mobile, Ala.
Burklund, Edwin C., 1517 St. Clair, St. Paul, Minn.
Burr, Louise Holmes, Permanente Hospital, 280 MacArthur Blvd., Oakland, Calif.
Cassels, Donald E., 920 E. 59th St., Chicago.
Chun, Lin Tung, King Kalakaua Bldg., Room 217, 1415 Kalakaua Ave., Honolulu, Hawaii
Copple, Bernard I., Tokyo General Hospital, c/o Postmaster, San Francisco
Cravens, James Hewitt, 1101 Maine St., Quincy, Ill.
Dew, Robert Ralph, 312 Bronson Medical Center, Kalamazoo, Mich.
Eberling, Ernest William, The Clinic for Children, Starkville, Miss.
Felknor, George Eckel, P.O. Box 29, Baytown, Tex.

Goldenberg, Erwin D., Kaiser Fontana Hospital, Fontana, Calif.
Green, William Roy, 5601 Old Mission Rd., Chattanooga, Tenn.
Hauser, Arnold E., 820 Marin St., Vallejo, Calif.
Hawkins, William Carter, 4325 Cole Ave., Dallas.
Hendrick, Jim Gilbert, 910 N. State St., Jackson, Miss.
Hill, Fontaine Sallis, 20 S. Dunlap, Memphis, Tenn.
Hoeck, LeRoy Edward, 108 19th St., S.E., Apt. 1, Washington, D.C.
Holt, Joseph Gordon, Jr., 306 Hamilton Bldg., Wichita Falls, Tex.
Humphreys, William Floyd, Jr., 112 E. Third Court, Panama City, Fla.
Johnson, Eloise Eberling, 314 Blakely Drive, San Antonio, Tex.
Keller, Frank Goulding, 1023 Dauphin St., Mobile, Ala.
Kelley, George Peyton, 224 Pennsylvania, Shreveport, La.
Kinberger, Frank Robert, 547 Esplanade Ave., New Orleans.
Korngold, Herbert W., 2524 Jay St., Sacramento, Calif.
Lipscomb, Joe L., 904 W. 7th Ave., Amarillo, Tex.
Luther, Gertrude C., Commercial National Bank Bldg., Anniston, Ala.
Madey, Stephen Laurence, 805 N. Blvd., Baton Rouge, La.
Mark, Jerome S., 4418 Vineland, North Hollywood, Calif.
McKemie, Jack F., Moody Clinic, 1611 Fifth St., Corpus Christi, Tex.
McLellan, Marion Smith, Jack Tar Court Hotel, Galveston, Tex.
McPherson, A. Ziegler, Physicians and Surgeons Clinic, Yazoo City, Miss.
Newman, Bruce Baxter, 4072 Hampton Ave., Western Springs, Ill.
Perkins, Georgia B., 4200 E. 9th Ave., Denver.
Rader, Guy Eugene, 817 E. Central Ave., Albuquerque, N.M.
Royce, Stephen Wheeler, Jr., 49 S. Catalina St., Pasadena, Calif.
Sanders, Lee H., 627 W. Jones St., Raleigh, N.C.
Sapper, Herbert Victor Louis, 525 N.W. 11th St., Oklahoma City, Okla.
Scull, Alvis Joe, Stanford University School of Medicine, Clay and Webster St., San Francisco
Shuttee, Robert David, 204 Bass Bldg., Enid, Okla.
Sisson, Thomas Randolph Clinton, 35 Chittenden Ave., Crestwood (Tuckahoe 7), N.Y.
Stepp, William Price, 376 S. Bellevue, Memphis, Tenn.
Syme, Oscar, 106 S. Girard Ave., Albuquerque, N.M.
Talley, Carolynn Downs, 1430 Tulane Ave., New Orleans.
Thomas, Daniel Martin, Medical Arts Bldg., Oak Ridge, Tenn.
Thompson, John W., 27 Eighth St., N.E., Atlanta, Ga.
Thorne, George Clifford, 607 W. 14th St., Austin, Tex.
Turnbull, Steve H., Jr., 1255 Eastmoreland, Memphis, Tenn.
Welsh, John B., 931 Meridian St., Anderson, Ind.
Williams, Lloyd Parrish, 110 N. Durkee St., Appleton, Wis.

The next oral examination will be held in Detroit on June 8, 9 and 10, 1951. This examination session replaces the one originally scheduled for Cleveland in June.

BOOK REVIEWS

YOUR CHILD MAKES SENSE, Edith Buxbaum, Ph.D., New York, International Universities Press, Inc., 1949, $3.25, 204 pp.

The author of this book is a practicing psychoanalyst working particularly with children and their parents in that she has collaborated with the pediatrician. The Foreword is by Anna Freud.

The author has been a popular lecturer for groups of parents and teachers and has led seminars on child development with various groups. The result is a well-written book, easy to read, realistic as well as theoretic, and although inclusive of many topics, it is not cumbrously lengthy.

Pediatricians as well as parents and teachers will find this book helpful in understanding the behavior of infants and children. It is difficult to find much with which to disagree in this book. One statement seems contrary to fact, namely, that stating: "Thumbsucking is in direct relation to sucking need. If the nursing time is sufficiently long and satisfying, thumbsucking usually does not occur or at least is temporary." Many clinicians will recognize this error from their own practices where infants have been adequately breast-fed and yet on occasion seem to have an extraordinary need for sucking of thumb and other objects.

In discussing the needs of the infant, the author does not lose sight of the fact that parents also have needs. Her presentation of child development is not one in which the child is considered in isolation as a neurologic or morphologic unit, but he is considered as a dynamic individual in relationship to other people particularly parents and siblings and school mates. The book ends with a list of reading references among which the pediatrician will find several old stand-bys written by members of his profession.

PSYCHOLOGICAL MEDICINE, edited by J. R. Rees, M.D., New York, Paul B. Hoeber, Inc., 1949, $10.00, 475 pp.

Written by 28 outstanding British psychiatrists and one American psychiatrist, this book consists of a collection of articles covering the field of psychiatry. It begins with a chapter on health which shows the author's eclecticism not only in matters of medical psychology but also of world health. The writer of that chapter is Director-General of the World Health Organization and his essay represents the close relationship between behavior and mental health to the problems of physical health. There follows in the book a chapter on the "Normal Individual," in which it is pointed out that there is a wide range of normality. The book from that point on presents material on subjects customarily presented in textbooks on psychiatry. For example, there are chapters on Abnormal Psychology, Intelligence, Personality Types, Psychosomatic Medicine, Anxiety States, Hysteria and the Obsessional States, Delinquency and Mental Deficiency, and the Depressions and Schizophrenia, and the Organic Reaction Types. Physical Methods of Treatment along with Psychotherapy and Medical Social Work are also discussed and the book ends with a classification of Psychiatric Illness.

For the American audience, this book has but one advantage over American textbooks; that is, that it gives professional workers on this continent an understanding of what is going on in the British groups of colleagues in the field of psychiatry. For the pediatrician there is one chapter which is outstanding, and that is one by Maberly, who was formerly Director of the famous Tavistock Clinic in London. The viewpoint of this author as he discusses development and care of the child is warm and sympathetic. Most of the emphasis in this chapter is on delinquent or truant behavior and on sex problems. Throughout the book the philosophy is based for the most part on psychoanalytic formulations and presents this in a modern and easily understood fashion.